Cost-effectiveness analysis of citalopram vs. escitalopram

A first-line treatment for major depressive disorder in Norway

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FOREWORD

The aim of this master thesis is to address the issue of whether replacing citalopram 20 mg daily by escitalopram 10 mg daily is cost-effective in Norway, using a health care payer and a societal perspective. The effectiveness data used in this analysis were supposed to be taken from the meta-analysis by The Norwegian Knowledge Centre for Health Services (NOKC, Project 340, *A systematic review of effectiveness of the antidepressants Selective Serotonin Reuptake Inhibitors (SSRIs) and other newer antidepressants*). As the NOKC's report will be finished in June 2007 and this master thesis is due on the 15th of May 2007, I had to search for the effectiveness data by myself. In the searching process, I got help from the librarian at NOKC's.

I would like to express thanks to nice people from NOKC for their help: Marianne Klemp Gjertsen, Aileen Rae Neilson, Sigrun Espelien Aasen, Morten Aaserud and Ellen Nilsen. Per Arne Holman (Lovisenberg LDPS) and Per Steinar Lund (Vitus Apotek), thank you for the cost data. To Jørgen Bramness (FHI) and Erik Hviding (LMV) for interesting discussions about antidepressants. Furthermore, thank to Iulia Ekeberg (Lovisenberg LDPS) and Lars Tanum (Diakonhjemmet Hospital) for their valuable comments on my model. And of course to my supervisor for his original and constructive criticism.

I am grateful that I have met these people during my life: Tvrtko, Vjerana, Zdravka, Zekanica, Damir, Bekim, Ela, Mirta, Zarko and Oldja family from Varazdin. Thank you for being my first-other family and supporting me in my good and bad times. I will never forget all fun, food, money and love that you gave me.

Than Jim, James and Nick, my dear Dudes. Joakim, Bente and Stein Runo who made my life in Oslo happier. Moreover, my worlds' best mum, for teaching me how to open my heart and how to laugh.

Ivar Sønbø Kristiansen was supervisor for this master thesis.

Zinajda Zolic

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ABBREVIATIONS AND ACRONYMS

APA	American Psychiatric Association
BDI	Beck Depression Inventory
CBA	cost-benefit analysis
CBT	Cognitive behavioural therapy
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CIDI	The Composite International Diagnostic Interview
CMA	cost-minimization analysis
CNS	central nervous system
CUA	cost-utility analysis
DA	dopamine
DALY	disability adjusted life year
DAM	decision analytic model
DDD	defined daily dose (of a drug)
DIS	Diagnostic Interview Schedule
DSA	deterministic sensitivity analysis
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECT	electroconvulsive therapy
HAMA	Hamilton Anxiety Scale
FDA	Federal Drug Agency
FHI	Folkehelseinstitutt (The Norwegian Institute of Public Health)
GP	general practitioner
HAMD-25	Hamilton Depression 25-item scale
HDRS	Hamilton Depression Rating Scale
HTA	health technology assessment
HUI	Health Utilities Index
ICD-10	International Statistical Classification of Diseases and Health Related Problems
ICER	incremental cost-effectiveness ratio

LDPS	Lovisenberg Diakonnale Psykiatrisk Sykehus
LOCF	Last observation carried forward
ITT	Intention to treat
MRI	magnetic resonance imaging
MS	multiple sclerosis
MDD	major depressive disorder
MAOi	monoamine oxidase inhibitors
MADRS	Montgomery-Åsberg Depress. Rating Scale
NA	noradrenalin
NOK	Norwegian crowns
OC	Observed cases method
OCD	Obsessive-compulsive disorder
PHQ-9	Patient Health Questionnaire 9-item
RCT	randomized controlled trial
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SSRI	selective serotonin reuptake inhibitor
SNRI	serotonin-norepinephrine reuptake inhibitors
SFD	symptom free day
TCA	tricyclic antidepressant
TDPS	Tøyen Diakonnale Psykiatrisk Sykehus (psychiatric hospital in Oslo)
TMS	transcranial magnetic simulating
VDPS	Vinderen Diakonnale Psykiatrisk Sykehus (psychiatric hospital in Oslo)
QALY	quality-adjusted life-years
WHO	World Health Organization

ABSTRACT

Background

Depressive disorders place a great burden on society and rank as the fourth leading cause of burden among all diseases. (WHO 2001) Antidepressants are the first-line treatment for major depressive disorder in Norway. Escitalopram (Cipralex®) is a patented antidepressant and therefore more costly than the generic drug citalopram. Since its introduction in the Norwegian market in 2002, the market share of escitalopram has increased sharply and accounted for NOK 131 mil in 2005. The same year, sales of citalopram were NOK 43 mil. By comparing costs and effects of the two drugs, an incremental cost-effectiveness ratio will indicate whether switching to escitalopram is a cost-effective option.

Methods

The study was based on a decision analytic model (decision tree) developed in Tree Age Pro Healthcare Module program for the adult Norwegian patients with major depressive disorder. Data used in the model consisted of costs and effectiveness data for citalopram and escitalopram. Cost data included relevant costs for each of the treatments from two perspectives: the health care payer perspective and the societal one. Effectiveness data were based on clinical trials. The time perspective of the model was six months. Health consequences were measured in terms of symptom reduction and translated into the quality-adjusted life years (QALYs). In one-way sensitivity analyses on all parameters, the results were, in the societal perspective, robust for all parameters except for the probability of a good response in the escitalopram group. When lower bound (0.39) was used for good response rate in escitalopram group, results have changed so that escitalopram was not cost-effective.

Results

The proportion of patients who had symptom reduction after six months increased by 5% (from 80% to 85%) by replacing citalopram with escitalopram. When indirect costs were taken into consideration (societal perspective), the cost per additional successfully treated patient was NOK 18 600. From the health care payer perspective, this cost was NOK 27 000. Assuming that one successful treatment is equivalent to 0.11 QALYs, the cost per QALY was NOK 169 000 and 245 000, respectively for the societal and health care perspective.

Conclusion

Escitalopram is a cost-effective option for treatment of major depressive disorder in Norway. This conclusion is valid for both the societal and the health care payer perspective.

1. Introduction

Increased trends in prescribing antidepressants from the 1990s until the present has increased health expenditures in Norway. (Figure 1) Introduction of the new class of antidepressants SSRIs that took place in 1990s has had an impact on this increase in expenditures. In 2005, sales of antidepressants in Norway were NOK 545 mil. (FHI 2006) Along direct costs related to depression, indirect (productivity) costs have increased too. Employed people who suffer from depression lose on average 11 working days during a 6-month period, twice that of employees who are not depressed. (Lepine, Gastpar et al. 1997) In 2006, the British Journal of Psychiatry published a study that estimated depression-related yearly costs for Norway on NOK 1,5 billions (Dalgard, McCracken et al. 2006)

High levels of public spending in Norway for depression emphasize the need for cost-effectiveness analysis of interventions for depression. The pharmacoeconomics of antidepressants are complex and there is lack of consistent methodology in this area. Another limitation is that different health care systems have different ways of financing health care. Economic evaluations until now have mainly compared psychological treatment versus antidepressants. There is still limited evidence of cost-effectiveness of antidepressants, to some extent due to lack of clinical evidence in head–to-head comparison of different drugs. (Barrett, Byford et al. 2005) Results of this analysis may contribute to better allocation of health care resources and more efficient and effective use of antidepressants in Norway.

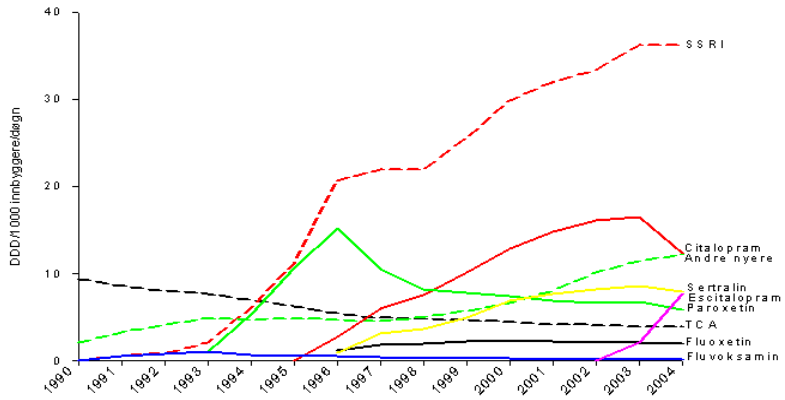

Figure 1 Sales of three major groups of antidepressants in Norway 1990-2004 in DDD/1000inh (The Norwegian Institute of Public Health) [1]

1 The approved antidepressants and their brand names in Norway (Citalopram=Cipramil®,Citalopram®. Sertralin= Sertralin® Zoloft®.

Escitalopram=Cipralex®. Paroxetin= Paroxetin®, Seroxat® Fluoxetin= Fluoxetin®, Fontex®).

This master thesis consists of an introduction (chapter one), description of methods (chapter two), results (chapter three) and discussion (chapter four). The definition, classification, diagnostics and epidemiology of depression are explained in chapter one. In addition, available treatments are described as well as the most used outcome measurements for depression. Furthermore, overview of the studies on cost-effectiveness of the antidepressants is given, for Norway as well as for the other countries. Comparators in the analysis and a decision tree are described, along the searching strategy used to select studies for model inputs. Results for each of the perspectives are presented, health care payer and a societal one, as well as sensitivity analysis results. Cost-utility analysis was performed in order to express result in terms of *cost per QALY gained*[2]. The discussion part summarizes main findings of my study, describe the strengths and the limitations and policy implications.

1.1. Definition, classification and diagnostics of depression

Major Depressive Disorder (MDD) is a chronic, recurrent illness associated with morbidity and mortality. It is the most common mental disorder and a major cause of disability in the world. It is the fourth leading cause of burden among all diseases and will have a growing trend during the next 20 years. (WHO 2001) By 2020, it may become the second most common cause of disability in the world. (Murray and Lopez 1996)

Mood disorders are classified into bipolar (manic, depressed, mixed) and unipolar mood disorder such as major depressive disorder (MDD). If MDD is the main diagnosis, further sub-classification depends on whether it is the first episode or a recurrence. When episodes of depression recur (between two episodes has to be at least six months) this is called recurrent depressive episode. A patient who has had two or more depressive episodes recently and has functional impairment related to MDD is considered to suffer from the recurrent depressive episode. (NICE 2004) It is difficult to draw a line between normal emotions (i.e. sadness, mood swings associated with person's unwanted life events, cultural/ social setting and personality) and a pathological condition. This makes classification and diagnosis in psychiatry very difficult. Diagnosis to a large extend depends on the physician's judgement of the patient as well as the patient's ability to make a distinction between depression symptoms and reaction to stressful life events.

[2] Quality-adjusted life year

According to the severity, depression can be mild, moderate and severe. Other important dimensions of depression are chronicity, recurrence and treatment resistance. The bases for the classification of the depression severity are scores from depression rating scales. The most used instruments administered by physician are the MADRS (Montgomery-Åsberg Depression Rating Scale) and the HDRS (Hamilton Depression Rating Scale). BDI (Beck Depression Inventory) that is the most used instrument in psychotherapeutic studies is a self-assessment instrument. (Åsberg, Bengtsson et al. 2004)

The diagnosis of depression assumes that a person's professional and personal life is, to a certain extent, affected by disease (depending on a severity level). Classification systems given in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) by The American Psychiatric Association require five out of nine symptoms for at least two weeks to diagnose a major depression.(APA 1994) WHO's ICD-10 (International Classification of Diseases and Impairments) categorize depression as mild, moderate and severe.

Mild depression does not disrupt usual activities. For diagnosis of mild depression, ICD-10 require the presence at least two out of three general symptoms that last for at least two weeks (certain deviation in mood, interest and energy level) and that cannot be explained by other physical or mental disturbance. (WHO 1992) In addition, one of seven additional symptoms has to be present as well: loss of self-confidence/self-esteem, feeling of inappropriate guilt/abnormal self-reproach, death/suicidal thoughts and/or self-destructive behaviour, lack of concentration and/or indecisiveness, slowing/agitation in usual activities, sleep disturbance and change in dietary habits that results in weight loss/gain.

Moderate depression includes mild depression criteria, along with six additional symptoms (out of the seven additional and three general symptoms) for at least a two-week period. A moderate depression episode often affects patient's ability to perform usual activities. A patient who has all three general symptoms and at least five out of seven additional ones has a diagnosis of severe depression, a disease that is dysfunctional in every way. (Goldman 2000) A patient that meets the diagnostic criteria for depression that lasts at least two years is having chronic depression. This depression can be mild, moderate or severe. (NICE 2004)

1.2. Epidemiology of depression

Reliable epidemiological studies allow better understanding of the depressive disorders. During their lifetime, around 10 percent of men and 24 percent of women in Norway will develop a severe depression; six to 13 percent of these will still have depression after two years. (Kringlen, Torgersen et al. 2001) Mild and moderate depression has been more common in the last 50 years while the incidence rate of the severe depression seems to be at a constant rate. (Åsberg, Bengtsson et al. 2004)

Are people more mentally ill or can the increase in the incidence rate of mild/moderate depression can be explained in a different way? An explanation for this increase can be assigned to various factors such as more resources used for research in medicine, easier access to health care services, more open communication between physicians and patients and influence of mass media on the people's perception of mental health (de-stigmatization). Furthermore, the pharmaceutical industry has financial and human resources that allow it to develop and market the new and effective drugs for depression. Prevalence of depression varies considerably across countries and among rural and urban areas. This is to some extent because studies in different countries have used different measures and sample selection procedures.

The European Commission established ODIN (Outcome of Depression International Network) in 1996 aiming to provide comparable data on prevalence and risk factors of depressive disorders in European rural and urban settings. The aim was further to assess the impact of two psychological interventions on the outcome of depression. Norway was one of the five countries in the ODIN study (the others being the UK, Ireland, Finland and Spain). This study was a cross-sectional two-phase community study. Instruments used were the BDI (Beck Depression Inventory) in Phase I and SCAN (Schedule for Clinical Assessment in Neuropsychiatry) in Phase II. The Norwegian rural setting was Rakkestad and the urban setting was Oslo. Studies have found a higher proportion of depression among the female population in urban areas. The prevalence was higher among women, as observed in previous studies. (Bebbington, Sturt et al. 1984; Weissman, Bland et al. 1996) Social, medical and genetic factors may explain this inter-gender difference in prevalence of depression.

The initial sample for Norway included 2444 individuals from the urban area and 2464 from the rural. The first phase completed 1456 individuals from the urban and 1594 individuals from the rural area. Out of these 53.9% were female in the urban area and 51.8 % female in rural area. Based on the results of this study, prevalence of depressive episode in Norway is 7% in the urban area (mean), CI 95% (4.6-10.4); and in the rural area mean is 8.4% (4.0-16. 8). Weighted prevalence of MDD (DSM-IV criteria) in urban area was 7% (4.7-10.2). Out of these 9.4% were females and 4.6% males. Rural area had prevalence of 8.48% (4.17-16.7). Out of these, 10% was prevalence for females and 5.81% for males. For comparison, the global sample of the five European countries had a total prevalence of 6.6% (5.4-8.4). Out of these 7.9% was the prevalence for females and 5.2% for males. (Ayuso- Mateos, Vazquez-Barquero et al. 2001)

The Lundby epidemiological study took place in 1947 in the Lundby area in the south of Sweden. It was designed as a prospective, longitudinal study on a total population of 3563 subjects over a 50 year time- period (1947-2007). Follow-up studies were carried out in 1957 and in 1972. In 1997 the surviving subjects (N=1797) were interviewed by psychiatrists with a semi-structured interview. The results showed that in both periods women had higher incidence rates than men. The average annual incidence rate was lower for women and tended to be lower for men in 1972-1997 as compared with 1947-1972. The cumulative probability for developing depression was 22.5% for men and 30.7% for women from 1972-1997. In the period 1947-1972, these figures were 22.8% for men and 35.7% for women. Lower annual incidence rates were observed from 1972-1997 than in period from 1947-1972. These findings suggest that the trend of increasing rates of depression in the Lundby cohort has ended. Incidence rates for depression were higher for women than for men, indicating importance of inter-gender differences. (Mattisson, Bogren et al. 2005)

Another two-phase epidemiological population study was carried out in Norway between 1989 and 1991 to assess occurrences of psychiatric diseases. A random sample included people from the Lofoten islands (rural area) and from Oslo (urban area). The first screening phase has completed 1879 persons who administered self- administered Hopkins Symptom Check List 25 items (HSCL- 25) and participated in an in-person interview. An HSCL-25 score greater than or equal to 1.55 indicated a “possible psychiatric case”. Out of 534 persons who met this criterion, 119 refused to participate in a second phase, thus 415 entered the second phase. A random sample of persons with the lower HSCL-25 scores was selected to

Phase II. Out of 263 persons, 61 refused to participate leaving 202 persons. Finally, 617 persons were interviewed with the Composite International Diagnostic Interview (CIDI). In this study a symptom score in HSCL-25 of 1.75 or more was found in 19.8% of females and 9.3% of males; ratio 2.1:1 (HSCL-25 score greater or equal to 1.75 indicates a psychiatric case). In addition, the number of cases was significantly higher in the oldest age group compared to the youngest.

There were no significant differences between rural and urban areas, but inter-gender and inter-age differences were present. Incidence rate for depression (ICD-10) was 2.6% in all ages (20-79), with CI 95% of (1.3-4.0). Out of these, females accounted for 4.3 % with CI 95% (1.8-6.8) and males 0.7% with CI 95% (0.1-1.4). The incidence rate of the first episode of psychiatric disorders was 2.7 (per 1000 persons per year). Incidence rate of depression, anxiety and somatoform disorders has increased significantly from 3.3 in 1930 to 12.8 in 1991. (Sandanger, Nygard et al. 1999)

Although the first depressive episode in most patients will spontaneously end after six months, depression has a strong tendency for recurrence and becoming chronic. Each new depressive episode increases the probability of a recurrent episode (after the first episode about 50% patients will have a second one, and about 70% of these will have a third episode). Intervals between episode occurrences are shorter every time. The problem is lack of long-term follow-up studies on primary care patients. Studies until now have shown significant gender (more women), age (aging and co-morbidity can partly explains this), ethnic (i.e. black/ Hispanic in USA or immigrants in Norway are more depressed) and geographical differences in incidence rates for depression.

Social differences have been observed too as depression can be related to poverty, constrained access to health care and illiterate people not able to understand and report illness. It seems clear that there is relationship between depression and other mental illnesses and/or other somatic chronic diseases (diabetes, MS, cancer, substance abuse, psychosis, schizofrenia). However, it is not clear whether or not the relationship is causal or structural (substance abuse as a cause of depression, depression as a cause of substance abuse, or none of these). Along with gender and income inequalities, culture is one important factor that differs between societies and has an impact on the epidemiology of depression. (Patel 2001)

1.3. Treatments for depression

Depending on severity (mild/moderate/severe) and type of depressive disorder (unipolar/bipolar), age of the patient (child/adolescent/adult/elderly) and medical history (presence of the psychiatric disorder in family) treatments for depression include antidepressants, psychotherapy, electroconvulsive therapy (ECT), phototherapy, alternative medicine or combination of these.

First-line treatment for depression is pharmacotherapy. The first effective antidepressant drug was discovered in the 50's. Iproniazid, a monoamine oxidase inhibitor (MAOi) was originally an antitubercular drug. Imipramine, tricyclic antidepressant (TCA), was developed in 1957. Both drug classes, MAOi and TCAs are interacting with the monoamine systems: amines: DA (dopamine), noradrenalin (NA or norepinephrine) and 5-hydroxytryptamine (5HT or serotonin). TCAs increase serotonergic function by blocking serotonin reuptake. Interesting is that drug was actually invented before the mechanism of the disease was discovered. During the 60's and based on the action of the drugs, scientists proposed an hypothesis in order to explain the cause of depression. Ashcroft believed that the lack of serotonin was the cause of depression. (Ashcroft, Crawford et al. 1966) In 1965, Schildkraut stated that noradrenalin might play a key role in the aetiology of depression. (Schildkraut 1965)

An abnormal function in the serotonin transmitter system can cause depression. The focus in treatment of depression has moved from turnover of neurotransmitters to receptor regulations and lately to intracellular changes. New generation antidepressants were designed as selective serotonin reuptake inhibitors (SSRIs). In 1993, Seroxat® (paroxetin) was the first SSRI introduced into the Norwegian market. Even though it is known that they have an effect on major neurotransmitters in the central nervous system (CNS), the mechanism of action of the second-generation antidepressants is poorly understood. Three main therapeutic classes of atidepressants consists of TCAs or *old generation antidepressants* while the SSRIs make the *new generation of antidepressants*. There is also a class known as *other newer antidepressants,* or serotonin-norepinephrine reuptake inhibitors (SNRIs). SSRIs are better tolerated than antidepressants of the old generation (TCAs), have fewer adverse effects and therefore fewer withdrawal symptoms. When compared to new generation antidepressants, TCAs do not differ in efficacy but in a poorer tolerability profile.

In 1968, Carlsson discovered that antidepressants can block the reuptake of serotonin and this discovery led to a development of a compound that selectively blocked the reuptake of serotonin, without acting on noradrenaline.

Such agents are known as SSRIs. In order to understand the mechanism of SSRIs, it is necessary to clarify terms such as synapse; link through which brain cells "communicate".

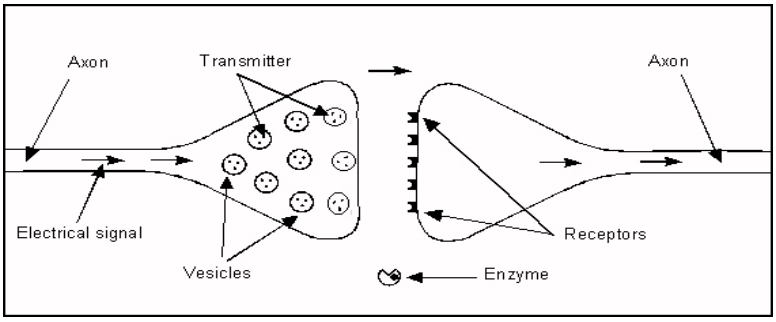

Figure 2 Transmission of information in the brain is taking place through synapse[3]

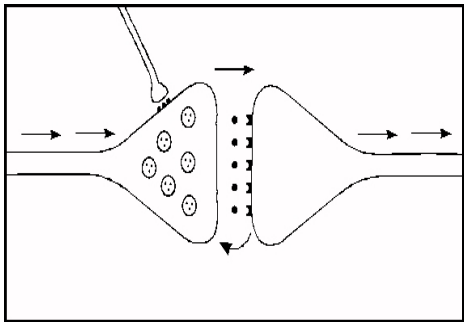

Figure 3 Nerve activity (not depressed)

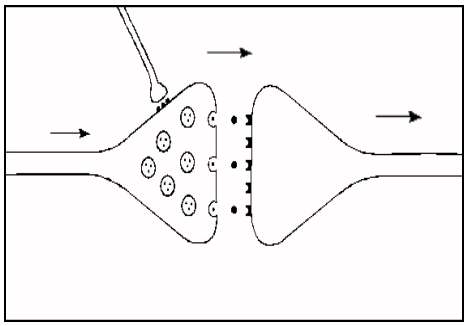

Figure 4 Reduced nerve activity (depression

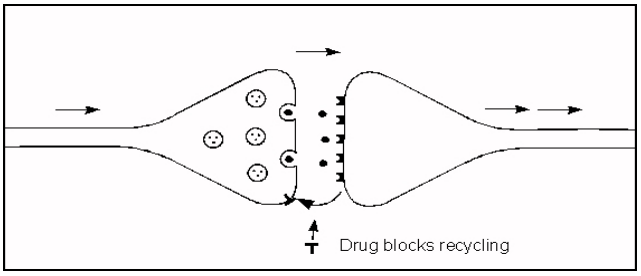

Figure 5 SSRI blocks reuptake of transmitters and increased messages passes.[4]

Figure 5, in a simplified way, illustrates a mechanism of SSRIs action. The hypothesis is that in some patients too little serotonin (or noradreneline) is the cause of a depressed mood. When a new impulse comes, there are more transmitters and a stronger message is passed.

3 Figures are from Norfolk&Waveney. (2007). "NWMHP Pharmacy Medicine Information." Retrieved 7.5.2007, from http://www.nmhct.nhs.uk/Pharmacy/.

Consequently, activity in that part of the brain is increased. SSRIs are supposed to correct the effect of the lack of transmitters.

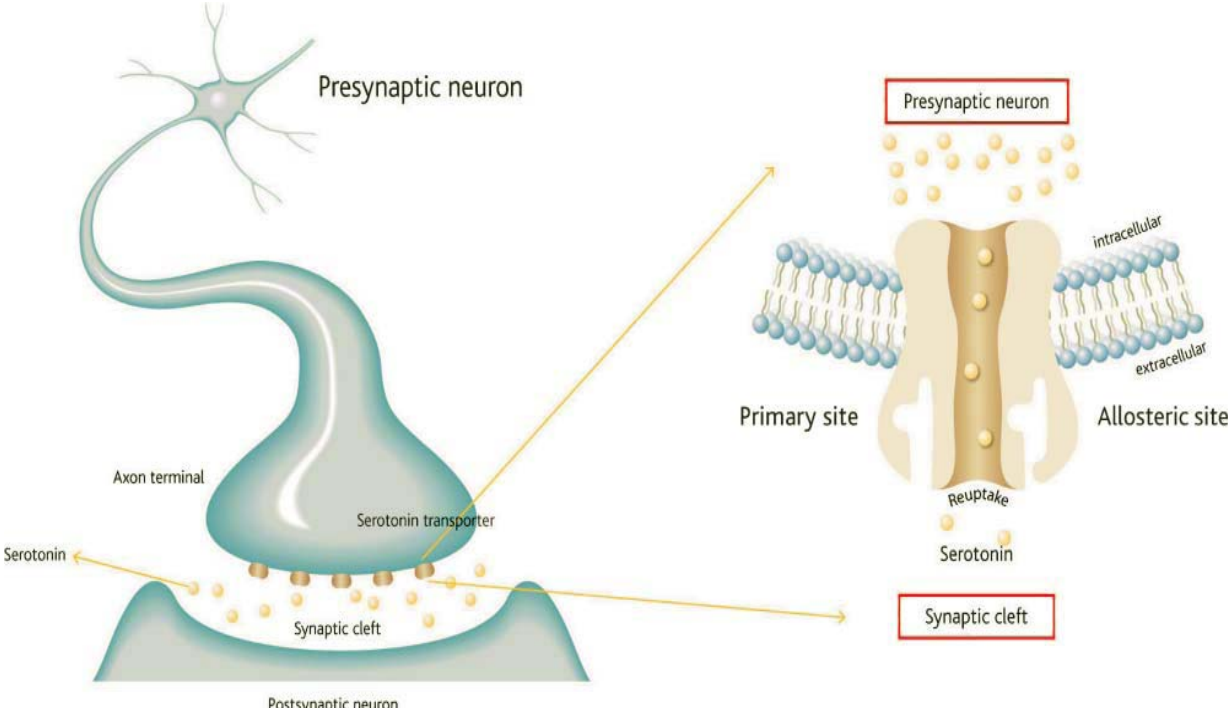

Figure 6 illustrates a synaptic gap between two serotonergic neurones. The nerve impulse "travels" to the postsynaptic neurone across the synaptic cleave due to the release of serotonin from the presynaptic neurone into the synaptic cleft. Molecules of serotonin are removed from the synaptic gap into the presynaptic neurone by the 5-HT transporters'. This reuptake process can be inhibited by compounds such as 5-HT reuptake inhibitors (SSRIs). (Sanchez 2006)

In 2000, Carlsson (University of Gothenburg, Sweden), Greengard (Rockefeller University, US) and Kandel (Columbia University, US) won *The Nobel Prize in Physiology or Medicine* for their half a century research in neuroscience. Carlsson's central discovery, that led to treatments of Parkinson's disease and schizophrenia, was that dopamine is a key neurotransmitter in the brain. Greengard has figured out the way on which dopamine and other neurotransmitters activate their target neurons when they attach to the synapse. Based on the findings of Carlsson and Greengard, Kandel has demystified important features of learning and memory. Further research on the connections between neurotransmitter levels and mental states led to discovery of antidepressants such as Prozac. (Stock 2001)

In patients who have serious psychosocial problems and/or did not respond well on drug treatment, psychotherapy can be an alternative to the drugs (cognitive, behavioural and interpersonal) and as effective as drugs. (Brown, Schulberg et al. 1996) In most of the patients for whom drug treatment is not sufficient, psychotherapy in combination with drugs can be the optimal treatment. In patients with severe, psychotic and manic episodes and only if other treatment options are exhausted (no remission or reduction of symptoms), ECT is required.

Various treatments for depression have been seen differently across cultures. The public views on the ECT and to the admission to the hospital negatively and people believe that these treatments are more harmful than useful. (Jorm 2000) ECT can be assessed as right unilateral (only on the right side of the brain, shown in trials as having fewer cognitive effects than bilateral) or as bilateral (both sides). (APA 2000) Bilateral ECT results also in rapid initial response and high rates of sustained response and remission. (Husain, Rush et al. 2004)

Other somatic treatments like magnetic seizure therapy and vagal nerve stimulation may be beneficial, but evidence is not sufficient to recommend its use in clinical practice. (APA 2000) Systematic review of psychotherapy and pharmacotherapy has concluded that combination of these two treatments is more effective than pharmacotherapy alone. (Pampallona, Bollini et al. 2004) The stigma that is associated with mental disorders can be a deterrent to seeking professional help. (Jorm 2000) A minority of people who meet depression diagnostic criteria will look for professional help. (Narrow, Regier et al. 1993)

Therefore, self-help such as physical activity, engaging in pleasurable activities and support from family and friends are of great importance. Due to lack of evidence of effectiveness of the self-help interventions, it is difficult to claim which are more effective. (Jorm 2000) Social support seems to be effective in mild depression (Bridges, Goldberg et al. 1992) as well as physical exercise. (Martinsen 1994)

St John's wort is proven effective in treating mild depression. Some other RCT have also shown St John's wort more effective than placebo, (Kalb, Trautmann-Sponsel et al. 2001) or more effective than antidepressants. (Schrader 2000) Contrary, other trials have not shown St John's wort to be more efficient than placebo (Shelton, Keller et al. 2001) or than other antidepressants. (Behnke, Jensen et al. 2002) Shared responsibility for depressed patients with regular and open communication between primary care physicians, psychiatrists, patients and

their family members is necessary. Further, disease management programs, telephone support and patient education can improve the effectiveness of drug treatment. More studies in the future should evaluate effectiveness of counselling, psychological treatment for severe depression and physical exercise in mild to moderate depression.

1.4. Outcome measurements for major depressive disorder

CEAs that compared interventions for depression used nearly 30 different outcome measurements (scales) to express effectiveness. Primary outcomes were depression-free day, quality of life, successfully treated patients, hospitalization, social adjustment and relapses avoided. Most of the studies have used the health care payer perspective for considering costs; few have used the societal one. (Barrett, Byford et al. 2005)

Commonly used outcomes related to MDD are presence of depressive symptoms; social and occupational functioning, quality of life, hospitalization, self-harm, relapse of depressive symptoms and adverse event rates. (Geddes and Butler 2002) The impact of major depression on patients' functioning and quality of life can be measured with the SF-36 (*Short Form 36*), Quality of Life in Depression Scale and the EQ-5D. (Sapin, Fantino et al. 2004) The "Guide to Treatments that Work" names trial outcomes in terms of symptom severity scales such as the Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HAMD-25) and Hamilton Rating Scale for Depression (HRSD). (Gorman 2002)

HRSD/HAMD-25 is observer-based disease-specific rating scale. The BDI is a patient-based disease-specific rating scale. The Quality of Life scale is a patient- based non-disease specific scale of global functioning. The Patient Heath Questionnaire, 9-item (PHQ-9), a newer depression severity scale, is brief and includes one functional status item. The Diagnostic Interview Schedule (DIS) and the MADRS are often used in the depression studies.

In this analysis, the main outcome is expressed as a dichotomous variable *symptoms reduced* and *symptoms persist*. Whether a patient (after six months treatment with citalopram or escitalopram) have depression symptoms reduction or not, depends on the difference in the MADRS score measured at the baseline and after week 24.[5] (Colonna, Andersen et al. 2005) MADRS is an depression rating scale that measures overall severity of depressive symptoms

by a brief 10-item checklist. A person who has at least 30 in MADRS score is considered to have major depressive disorder. This score is one of the conditions for a person to enter a clinical trial with antidepressants. The Hamilton Anxiety Scale (HAMA or HAS) is a 14-item test that measures the severity of anxiety symptoms in children and adults. It is also used in measurement of the efficacy of the medications for anxiety. This instrument measures overall, somatic and psychic anxiety.

CGI-S scale is a three-item scale used to assess treatment response in psychiatric patients such as severity of Illness, global improvement and the efficacy index. Item one is rated on a seven-point scale (one is normal, seven extremely ill); item two on a seven-point scale (one is very much improved to seven very much worse) and item three on a four-point scale (from none to good therapeutic effect). The Global Improvement item requires the clinician to rate how much the patient's illness has improved or worsened relative to a baseline state. Compared to the condition at baseline, a patient's state is compared to change over time, and rated from the very much improved to the very much worse.

Severity of illness rated on the CGI scale is based on the rater's subjective views of symptom severity, which can make interpretation of scores difficult. (Spearing, Post et al. 1997) For this reason, I have not used CGI-S outcome data that was used as a secondary outcome measurement in the trial by Colonna. (Colonna, Andersen et al. 2005)

1.5. Earlier research on the cost-effectiveness of antidepressants

To find previous research on CEA of antidepressants, I have performed literature search in October 2006. Databases searched for cost-effectiveness studies on antidepressants were[6] The Cochrane library, PubMed, NHSEE Database (National Health System Economic Evaluation Database), HTA Database and CCOHTA (Canadian Coordinating Office for HTA). Search filter consisted of terms such as *cost, depression, antidepressant, SSRI, SNRI and TCA*. These terms were combined with terms such as *health technology assessment, pharmacoeconomic, economic evaluation, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, and cost of illness*. Filter for date of publication was not limited at the beginning.

5 If a patient has MADRS score ≤12 at week 24, patient has symptoms reduced. If MADRS score is >12, patient has symptoms persist.

6 For the search results see Appendix I

After I have narrowed my research question to citalopram and escitalopram, further literature search was from year 2002 since escitalopram was introduced into the market that year.

Most of the relevant analyses found have used costs combined with a single disease-specific outcome measure, e.g. score from depression scale. Clinical efficacy of the SSRIs is similar to TCAs; except that SSRIs are associated with lower rates of non-compliance and treatment discontinuation attributed to adverse effects. (MacGillivray, Arroll et al. 2003) CEA of escitalopram vs. venlafaxine in Germany resulted in cost-effectiveness of escitalopram. (Kulp, von der Schulenburg et al. 2005)

Pharmacoeconomic analysis of the cost-effectiveness of escitalopram vs. citalopram, fluoxetine, venlafaxine XR and sertraline was carried out for Finland, Norway, Sweden, Belgium and UK. The year of costing was 2000-2001 and the decision analytic models had a 6-month time horizon. These studies' results have shown that escitalopram is the more cost-effective option from the health care provider perspective. (Croom and Plosker 2003)

These studies have limitations such as lack of head-to-head clinical trials comparing escitalopram to the other drugs. Model inputs for effectiveness data used in these studies are the main limitation in identification of the more cost-effective strategy. Studies that compared venlafaxine (SNRI) vs. SSRIs have favoured SNRI over SSRIs in terms of cost-effectiveness. (Doyle, Casciano et al. 2001) Gorman's pooled analysis of 1321 patients that participated in the three placebo-controlled trials for efficacy comparison suggests that escitalopram may have faster effect on symptoms than citalopram. (Croom and Plosker 2003)

However, Svensson criticizes Gorman's analysis for not being transparent in randomization and double-blinding method. The pooled analysis did not present a main outcome but stated that the main outcome in the three-pooled trials was the mean change in MADRS score from baseline to week eight. The analysis was performed on patients who had received at least one dose of double-blind medication and had at least one post-baseline MADRS assessment (intention-to-treat ITT). The proportion of randomized patients from the each group that were not included into ITT population (because of dropping out before the first post-baseline assessment) was not reported.

Where there was no significant difference between citalopram and escitalopram, the authors described the results with positive phrases as *trend toward significance* and *trends in favours*

of escitalopram. Analysis mentions six comparisons where citalopram was not superior to placebo but no comparisons where escitalopram was not superior to placebo. (Svensson and Mansfield 2004)

Although SSRIs appear to be a dominant option over TCAs in many patient groups, available evidence on which conclusions are drawn is not strong enough to identify the cost-effective strategy. (Barrett, Byford et al. 2005) The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) conducted a systematic review of the cost-effectiveness of SSRIs compared to TCAs. The main finding was that no antidepressant is a less costly and more effective option. (CCOHTA 1997)

Studies that have examined cost-effectiveness of adding counselling to usual care by a GP have not found significant differences in costs or effects at the long-term follow-up. (Miller, Chilvers et al. 2003; Simpson, Corney et al. 2003) As these studies were measuring clinical efficacy of counselling, they might have limitations in identification of significant differences in costs. Economic evaluation of couple therapy compared to antidepressants for MDD patients has shown couple therapy as cost- effective option. (Leff, Vearnals et al. 2000)

Another meta-analysis of 20 studies and 1020 patients concluded that there is no significant difference between escitalopram and other antidepressants on increasing the likelihood of remission measured by the MADRS scale. (APA 2000) More than 30 outcome scales used in studies makes it difficult to compare results across different studies and interventions. (Barrett, Byford et al. 2005) Many studies considered only a narrow definition of costs; considering broader costs in depression intervention is of greater importance. There is evidence that remission of depressive symptoms more rapidly affects employment status than health care service utilization. The economic consequences of depression are influenced mainly by the presence of medical co-morbidity than by symptom severity alone. (Chisholm, Diehr et al. 2003)

Comparability across economic evaluations is difficult due to large variations in the range of costs. In addition, the absence of the standard treatment or universal form of usual care in different countries limits comparison between studies and cause the problem of external validity. Results from economic evaluations are dependent on assumptions of the model and the effectiveness and cost data chosen for the input. In a systematic review of the CUA in the

management of depression, pharmacologic interventions generally had lower costs per QALY gained when compared to non-pharmacological interventions. When compared to usual care, psychotherapy alone, care management alone and combination of psychotherapy and care management had lower costs per quality adjusted life year (QALY) gained.
Generally there is a lack of cost-utility analyses (CUA) in depression studies (e.g. from 539 CUA at Harvard Centre for Risk Analysis Cost-effectiveness Registry, only one is of depression management). (Pirraglia, B. et al. 2004) None of the CUA, until now, was comparing citalopram and escitalopram. Different outcome scales used for effectiveness, absence of standard treatment for MDD and difference in health care systems makes generalization of results difficult for the other countries.

1.6. Citalopram and escitalopram

New drugs are often a single enantiomer of the existing drug. As the old drugs reach the end of their patent life, manufacturers are interested in the production of the single enantiomer equivalents, claiming better effectiveness and patenting a new drug. This is known as a *chiral switching* and is claimed to result in improved efficacy and reduced toxicity. Patent protection and a awareness of advantage based on promotion rather than clinical evidence will maintain high price for single enantiomer drugs. (Mansfield, Henry et al. 2004) Single-isomer drugs make up more than fifty percent of the top selling 100 drugs worldwide.[7] (Svensson and Mansfield 2004) Molecules of citalopram consist of equal amounts of an S- and an R-enantiomer (mirror-forms).

Pharmacological studies have shown that SSRI activity of citalopram resides almost entirely in the S-enantiomer. (Hyttel, Bogeso et al. 1992) By isolating S-enantiomer from citalopram, new drug escitalopram was patented in 2002.

S-enantiomer has the highest selectivity for the human serotonin transporter relative to the noradrenalin (NA) or dopamine (DA) transporters. (Owens, Knight et al. 2001) In the process of isolation of S-enantiomer from citalopram, the assumption was that S-enantiomer, due to its therapeutical activity, would have the same efficacy as citalopram, but at half of the dose. The tolerability profile of escitalopram is similar to that of citalopram. (Waugh, Goa et al.

7 Citalopram (Cipramil®) was accounted for 78% of Lundbeck's total turnover in 1999. Lundbeck. (2007). "Company History 1990- 2000." from http://www.lundbeck.com/aboutus/history/companyhistory/1990/default.asp.

2003) Nausea is the most common adverse event of escitalopram. (Croom and Plosker 2003) Some RCTs suggest that escitalopram is superior to a placebo in the short-term treatment of depression. (Burke, Gergel et al. 2002)

Citalopram is a generic drug, reimbursed in Norway under the brand names *Cipramil* (Lundbeck), *Apertia* (CNSpharma), *Citalopram* (Alpharma), *Redoxamin* (CNSpharma), *Citalopram Ratiopharm* (Ratiopharm), *Citalopram Teva* (Teva) and *Cipramil* (Farmagon).[8] It is produced as 10, 20 and 40 mg tablets. Escitalopram is a reimbursed drug patented by Lundbeck in 2002. Escitalopram under the brand name *Cipralex* is produced by Lundbeck, Farlic and Orifarm. It is produced as a liquid (drops) 10 mg/ml and in tablets of 5, 10 and 20 mg. Citalopram and escitalopram are drugs used for treatment of depressive disorders.

Pharmaceutical companies that fund clinical trials tend to compare drugs to placebo because this study design gives higher chance that the drug will be demonstrated as efficient when compared to another drug of the same class that is generic, less costly and in many cases similar in effectiveness and efficacy. However, escitalopram was not more effective, safer or better tolerated than citalopram. (Masilamani, Ruppelt et al. 2003)

Further studies are needed aiming at the comparison of the therapeutic efficacy of escitalopram with other antidepressant drugs in different patients and the assessment of the effect of the drug on cognitive functions. Escitalopram can therefore be understood a ‘chiral chimera’. (Svensson and Mansfield 2004)

1.7. Objective of the analysis

[8] From www.legemiddelverket.no

The objective of this study was to answer the research question what are the incremental (additional) costs and health consequences of replacing citalopram 20 mg with escitalopram 10 mg. The method used was a decision analytic model and the period of the analysis is six months. By comparing costs and effects of citalopram and escitalopram in a decision tree model, an incremental cost-effectiveness ratio (ICER) of replacing citalopram by escitalopram was calculated. Analysis was performed from the health care payer and a societal perspective. Besides a health care payer perspective, a societal perspective is taken because depression has strong impact on patient's ability to work and productivity costs have to be included into analysis. Furthermore, this often affects their families' members.

Table 1

INFORMATION ABOUT ANALYSIS	
Research question	What are the incremental costs and health consequences of replacing citalopram 20 mg with escitalopram 10 mg
Analysis	Cost-effectiveness analysis
Program used	Tree Age Pro Healthcare Module 2005
Analytic model	Decision tree
Patient	Depressive disorder (DSM-IV), outpatient, male/female, age 18-65
Intervention (baseline)	Citalopram 20 mg
Comparator	Escitalopram 10 mg
Primary outcome measure	*Symptoms reduced* (MADRS score ≤12 at week 24) and *symptoms persist* (MADRS score >12 at week 24)
Time perspective	6 months
Use of health care resources	Expert opinion
Unit costs (for Norway)	Market prices (drugs), fee schedules, empirical costs data from the three psychiatric hospitals in Oslo

2. Methods

2.1. Decision model description

In this analysis, the decision tree examines the cost and health outcomes associated with two treatment options (citalopram and escitalopram) over a six-month period in Norway. Parameters for the model are based on the RCTs, systematic reviews, clinical guidelines for MDD (Anderson, Nutt et al. 2000; APA 2000; Legemiddelverket 2004; NICE 2004; UMHS 2005) and expert opinion.[9] Based on this information, I have developed decision analytic model.

The decision tree presents two treatment options, one main branch (strategy) for citalopram and the other for escitalopram (Figure 5). The model was developed in the Tree Age Pro Healthcare Module 2005 program. Pathways through which patients may flow are identical for both alternatives. However, probabilities for each of the pathways are different for two drugs and that, along the difference in the resource use, will have impact on results. Results will be expressed as a *cost per patient with symptom reduction*.

In the decision tree, there are three main node types: circle represents *probability node* (or chance), square represents a *decision node* and at triangle at the end of each pathway is a *payoff node* (terminal). Terminal node (payoff) is the point with the all costs and effects that appear from the root node up to payoff node. After six-month period (time of the analysis), patient will end up in *symptoms reduced* or *symptom persists* health outcome**.** Other studies have used terms such as "depression free", "successfully treated patient", or "remission" and "relapse" as the health outcomes.

Considering the course and the nature of depression, I wanted to avoid terms like "depression free", since studies and clinical practice have shown that about 50 percent of depressed patients who have an initial depressive episode will have recurrence (second depressive episode) and out of these, 70 percent will have a third episode. Therefore, I believe "symptom reduced" is the more accurate description of what has been measured with MADRS score. An economic evaluation for antidepressants in Norway used "remission" and "relapse" for the health outcomes. (Francois, Toumi et al. 2003) I argue that in order for depressive episode to

be considered as "relapse", time from the previous episode has to be at least six months. Since that model is for six-month period, this health outcome should not be labelled as "relapse". Patient can have remission in symptoms after six months, but cannot have relapse after six months.

The *root node* of the model starts with patients who are candidates for treatment with citalopram and escitalopram. The criterion include diagnosis of MDD (DSM-IV diagnostic system, MADRS score ≥22 and <40 when entering the trial, called *baseline*), adult (age over 18 but less than 65), not suffering or having history of any other mental disorder, not using any other antipsychotic, anxiolytic, anticonvulsant drugs or substance abuse. Furthermore, patient cannot have other chronic disease(s) and cannot be pregnant.

First, patients in the model receive one daily-defined dose of citalopram (20 mg) or escitalopram (10mg) in primary care. A clinician makes this decision. After receiving citalopram or escitalopram for 8 weeks (the time SSRIs need to *work*), clinician will evaluate patients for the first time after receiving the treatment. The evaluation is based on difference in MADRS score from the baseline to week 8. The MADRS score is the primary parameter of antidepressant efficacy. If the score has improved by at least 50 percent from the baseline, patient is in *responder* group. At this point, some of the patients dropped out from the study. Other may have no response to the drug, or they may suffer from very unpleasant and strong adverse effects. Some of the patients will have a good response to the drug. For each of these possible pathways, probabilities are collected from clinical data and are assigned for each of the drug. Based on the evaluation of the patients, the clinician will suggest further treatment strategy.

As one could expect, patients who have a good response will continue the same treatment on the same dose. Patients who had no response to the drug can switch to another antidepressant (as recommended to switch to serotonin-norepinephrine reuptake inhibitors SNRI) or can stay on the same drug (citalopram/escitalopram) but on an increased dose (citalopram increased on 28 mg and escitalopram 14 mg based on titration clinical data). Some of the patients with intolerable adverse effects will discontinue treatment and be referred to a specialist (secondary care), and some will be switched to SNRI. Patients who do not have relief of the symptoms after switching to the SNRI (due to non responding to drug or having serious

9 GP currently working in the hospital, specialization in psychiatry interviewed in April 2007, psychiatric hospital in Oslo

adverse effects), are referred to the secondary care (specialist care in Norway). After the GP refers a patient to a specialist, about 10 percent of the patients will need inpatient care (hospitalization), mostly because of self-harm or suicidal thoughts that occurred. The other 90 percent will be treated in the outpatient specialist care.

In the clinical practice some of the patients can have a partial response to the drug (efficacy is not sufficient). In the model these patients will be classified as *no response*, since treatment strategy after *no response* or a *partial response* is the same (*switch drug* or *increase dose*). Some authors included suicide risk into effectiveness studies of SSRIs. (Demyttenaere, Hemels et al. 2005) Although suicide is mentioned often in literature as adverse effect of SSRI and it is important public health problem, I assumed that there would be no difference in suicide risk between citalopram and escitalopram.[10] As we are interested in *incremental* costs and effects between two drugs, a suicide risk is not included into the model.

Table 2 Basic model characteristics

Treatment aim	Reduction in symptoms
Model time	Six months
Outcomes	*Symptoms reduced* (MADRS score ≤12 at week 24) and *symptoms persist* (MADRS score ≥12 at week 24)
Drop out	Discontinued treatment due to intolerable adverse effects
Increased dose	14 mg for escitalopram (40% increase from DDD) and 28,4 mg for citalopram (42,3% increase from DDD) (Lepola, Loft et al. 2003)[11]
Switch to SNRI	If SSRI is not well tolerated, patient is switched to SNRI (venlafaxine)
	Before prescribing venlafaxine, ECG is recommended (cardio-toxicity)
Resource use assumption	Four GP visits are required during maintenance period of 6 months in order to prevent relapse
Discounting	No discounting, due to <1 year time horizon
Maintenance	Continue treatment for 6 months after remission, to prevent recurrence

10 Moore et al 2005

11 Mean dose increase in the study that compared efficacy of the flexible doses of citalopram and escitalopram.

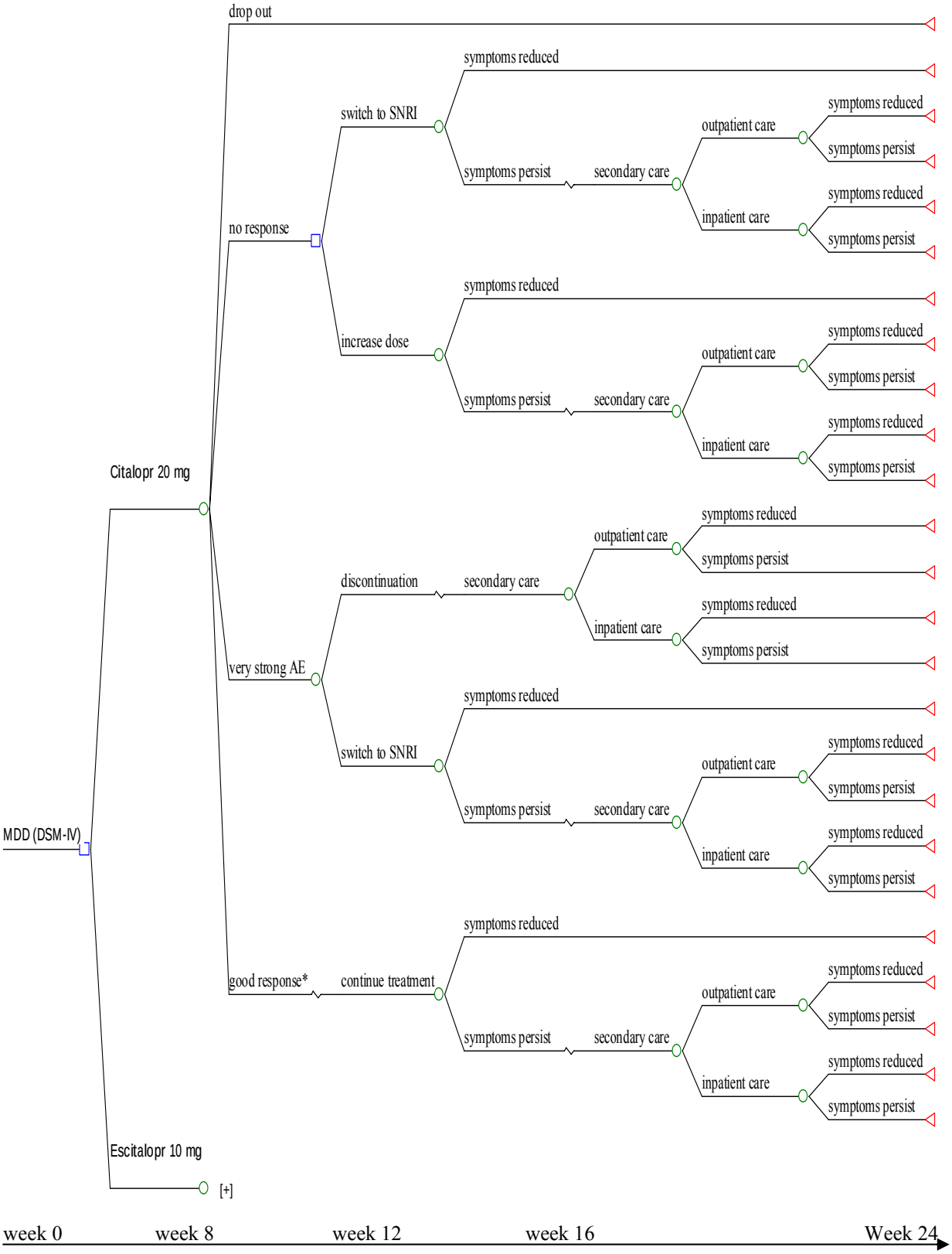

Figure 7: The model structure[12]. (*Tree Age Pro Healthcare Module 2005).*[13]

12 The structure of the escitalopram node is identical as a citalopram node, with different probabilities.

13 §=out of 1/2 patients that have some kind of AE, 10-20 % will have so strong AE that will lead to change in treatment strategy. *=symptom reduction >=50% MADRS score, from the baseline to week 8.

2.2. Measure of effectiveness

Effectiveness data were collected from the review of the relevant literature (see Appendix I, search results). In the 24-week head-to-head trial of citalopram and escitalopram, patient at the baseline had MADRS score ≥22 and <40. The remission rate is defined as MADRS score ≤12 measured at week 24 (Colonna, Andersen et al. 2005). In this model, *remitter* has the *symptoms reduced* outcome*.* Value of one (1) was assigned to this outcome. Patients who do have MADRS score greater than 12 have a *symptoms persist* outcome*,* with assigned value zero (0). In these patients, symptoms of the depression are still present after six months. The assumption is that 20 percent of the patients from the secondary care will not have symptom reduction after the six-month treatment. If this depression continues for another year and a half, patient has a chronic depression. In order to avoid relapse, patients that have *symptom reduction* should continue with the same treatment for the next six months and visit GP four times (maintenance therapy). An example of the MADRS instrument is in Appendix IV.

2.3. Probabilities

The review process aimed at collecting effectiveness data was performed through developing a search filter (MeSH term index database) and searching procedure that included RCTs (randomized controlled trials), systematic reviews (meta-analysis), economic evaluations and head-to-head trials on citalopram and escitalopram. Out of selected studies, inputs for a model are chosen based on quality of the studies. (Table 3, page 30). Inclusion criteria were RCT on efficacy, safety, effectiveness and/or tolerability of citalopram and escitalopram. Literature on effectiveness data was searched from October 2006. Studies that were rated as *poor quality* in systematic overviews were excluded. Databases searched were BMJ Clinical Evidence, The Cochrane Library, DARE (Database of Abstracts and Reviews of Effects), Centre for Reviews and Dissemination Databases, NHS EE Database (National Health System Economic Evaluation Database), HTA Database, CCOHTA (Canadian Coordinating Office for HTA), EMBASE, PsycINFO, SBU (The Swedish Council on Technology Assessment in Health Care), Oregon Evidence Based Practice Centre, PubMed.[14]

14 All databases can be found on the www.helsebiblioteket.no

A selection of the clinical evidence for model inputs

Findings from the Oregon Evidence-based Practice Centre in general favoured escitalopram over citalopram. (Gartlehner, Carey et al. 2006) Two studies reported statistically significantly higher response rates for escitalopram than for citalopram (76.1% vs. 61.3%, $p<0.05$ and 63.7% vs. 52.6%; $p = 0.021$[15]). In both studies, escitalopram also led to higher remission rates than citalopram.

One trial was a fair-rated European/Canadian flexible dose study that compared the efficacy and tolerability of citalopram (20-40 mg/d) to escitalopram (10-20 mg/d) and placebo in 471 depressed outpatients attending primary care centres. (Lepola, Loft et al. 2003) ITT results showed that the escitalopram group had significantly more responders[16] (63.7% vs. 52.6%; $p = 0.021$) and remitters[17] (52.1% vs. 42.8%; $p<0.036$) than the citalopram group. Escitalopram was numerically (not statistically) better on three efficacy scales (MADRS, CGI-I, CGI-S).

The fourth study was a good fixed dose trial (escitalopram 10mg/d, citalopram 20 mg/d) in 357 European primary care patients over 24 weeks. Escitalopram patients had significantly higher response rates at week 8 (63% vs. 55%; $p<0.05$) but not at week 24 (80% vs. 78%; p=NR). (Colonna, Andersen et al. 2005) A pooled analysis of data from three RCTs concluded that escitalopram significantly improved sleep disturbance compared to citalopram. (Lader, Andersen et al. 2005)

There has been a lack of follow-up studies beyond six months. RCTs on citalopram and escitalopram lasted from four to 12 weeks. Only one good quality study lasted for 24 weeks (6 months).[18] Many adverse effects (including suicide) may occur after this period. More RCTs in the future and reports from patients about drug toleration may show some adverse effects that are yet unknown.

15 Results are for escitalopram vs citalopram

16 Responder is a patient that has a ≥ 50% reduction in MADRS score at week 8, from the baseline

17 Remitter is patient that has MADRS score <12

18 Colonna et al 2005

Table 3 Fair/good quality randomized controlled trials for citalopram and escitalopram

Author/year	N/ w[19]	Results	Quality[20]	Health outcome measurement	Source
(Burke, Gergel et al. 2002)	491/8	No sign. differ. between cital and escit.	Fair	MADRS, HAM-D, CGI-S, HAM-A, CES-D, QOL. Mean change in score from baseline to week 8.	[21] [22]
(Colonna, Andersen et al. 2005)[23]	357/24	More responders remitters in esc group at 8 weeks (but not at week 24)	Good	Mean change in MADRS score from baseline to week 24 Additional: CGIs and HAMa	[18]
(Lader, Andersen et al. 2005)	1321/8	No sign diff in mean MADRS score.	Fair	MADRS (cital, escit, placebo)	[18]
(Lepola, Loft et al. 2003)	471/8	Sign. More resp and remit in the escital group Esc>Pla Cit=Pla	Fair	Mean change in MADRS, CGI-S, CGI-I. Baseline, weeks 1,2,3,4,6,8	[18,19]
(Moore, Verdoux et al. 2005)	280/8	Sign. more responders and remitters in the escitalopram group	Fair	MADRS, CGI-S score. Baseline and weeks 1,4,8.	[18]

All trials were limited to male and female outpatients aged <65 years who met DSM-IV criteria for a first episode of a major depressive disorder, and had a MADRS score ≥22. Trial by Colonna included 357 adult patients, all aged <65 years. (Colonna, Andersen et al. 2005) This might mean violation of generalisability since aging population (especially in Norway) represents large group of antidepressants users.

The probabilities for the model in this analysis where adopted from trial by Colonna (no response, drop out due to adverse effects, adverse effects, good response). Despite of limitations, this trial was the only one with *good quality* rating (meta-analysis by Oregon group), had the longest duration of 24 weeks and large number of patients (n=357). In addition, patients were from the seven European countries including Norway, and that may favour internal and external generalisability of the results. The main outcome measure

19 N= number of patients in the trial. w=nr of weeks of the clinical trial

20 Quality rating as given in systematic overview, footnote 18.

21 Åsberg M et al. 2004

22 Gartlehner G et al. 2006

23 Probabilities for the model are choosed from this trial

(MADRS score at baseline and week 24) was not significantly different between escitalopram and citalopram. In the model, same main outcome measure was used.

Table 4 Probabilities used in the analysis

PROBABILITY*	CIT	ESCIT	REFERENCE
No response (at week 8)	0.45	0.37	(Colonna, Andersen et al. 2005)
Drop out (AE)	0.10	0.06	(Colonna, Andersen et al. 2005)
Adverse effects	0.14[24]	0.13[25]	(Colonna, Andersen et al. 2005)
Good response[26]	0.31	0.44	Footnote 12
Discontin. due to AE	0.3	0.3	Expert opinion
Sympt.red. after discontin.	0.7	0.7	Footnote 13
Sympt.pers after discontin.	0.3	0.3	(Wade, Toumi et al. 2005)[27]
Switch after strong AE	0.7	0.7	Expert opinion
Sympt. red after switch[28]	0.45	0.45	(Posternak, Zimmerman et al. 2001)
Sympt. persist after switch	0.55	0.55	(Posternak, Zimmerman et al. 2001)
Inpatient care (hospit.)	0.1	0.1	Expert opinion[29]
Outpatient care	0.9	0.9	Expert opinion
Sympt.red. after oupatient	0.8	0.8	(Hale 1997)
Sympt.persist after outpat.	0.2	0.2	(Hale 1997)[30]
Sympt.red. after inpatient	0.8	0.8	(Hale 1997)
Sympt.per. after outpatient	0.2	0.2	(Hale 1997)
Sympt.red.after good resp.	0.6	0.6	Expert opinion (footnote 30)
Sympt.per. after good resp.	0.4	0.4	Expert opinion[31]
Sympt.red.after dose incr.	0.43	0.52	(Lepola, Loft et al. 2003)
Sympt.pers. after increa.	0.57	0.48	(Lepola, Loft et al. 2003)

*Lower and upper limit used for the sensitivity analysis of the parameters are in the Appendix III.

24 Assumption: 1/5 of patients that have any of the AE will change/discontinue treatment. Cital.group 72%(any AE)*20%(1/5)=14.4=0.14

25 Escit. group 62.9%(any AE)*20%(1/5)=12.58= 0.13

26 (0.45+0.10+0.14=0.69) than 0.31 is left for good response. Same method used for escitalopram.

27 Rate used in this study was 27.5. Expert agreed on 0.3 as realistic rate.

28 44.7% of patients had positive response after switching (Posternak&Zimmerman 2001, table 4).100-44,7=55.3% will not have remission after switched drug

29 10% of the patient with depression will be hospitalized due to self-harm or suicidal thoughts or intentions. Same assumption was used in Wade et al 2005

30 20% of patients will develop chronic depression

31 This is called a **rebound effect** (patient going to improvement due to placebo and back to symptoms). 40% of the patients will have a significant return of the original symptom(even after having good response to drug in the first 8-12 weeks)

Table 5 Resources used in the model with the range for sensitivity analysis

PARAMETER	UNIT	L[32]	U[33]	REFERENCE
Frequency of specialist consult. when patient is hospital.	6	3	9	assumption
Frequency of GP visits during maintenance	4	1	6	guidelines
Frequency of GP visits when symptoms are reduced	2	1	4	guidelines
Frequency of GP visits when symptoms persist	4	2	8	guidelines
Frequency of specialist visits when symptoms are reduced	2	1	3	assumption
Number of days on afipram (against nausea)	14	7	30	assumption

2.4. Costs

The costing process in economic evaluation has three phases: identification of resources (costs) that are related to the health care program and for the perspective taken, measurement of resource use (quantities of resources required for each of comparators in analysis, or *frequency* of use) and the cost valuation phase (assigning prices for identified and measured resources).

In the cost identification phase, costs relevant to the health care payer and a societal perspective of both alternatives are identified. To identify costs it was necessary to assess which health care services/products depressive patients used (through the six months, and during maintenance phase if symptoms were reduced), in both primary and secondary care. For the *health care payer perspective*, these costs included diagnostic procedures, GP consultations, specialist consultations, inpatient care (hospitalization), drug costs, outpatient care, and maintenance costs. Indirect costs arise from the patient's inability to function normally and that result in a decrease in productivity.

Along costs from the health care payer perspective, productivity costs (day lost from work due depression) are added into *societal perspective*, with different frequency for primary and a secondary care. Cost data used in this model comes from primary data (average costs from the three Norwegian psychiatric hospitals)[34] and from secondary data (SSB, Norwegian Medicince Agency, GP and specialist fee schedules 2006-2007)

32 Lower limit for the sensitivity analysis

33 Upper limit for the sensitivity analysis

34 These data will be published in the master thesis of Holman PA in 2007, University of Oslo

Table 6 Costs in NOK for 2006/2007, used in model for the Norwegian setting

COST ITEM	NOK	L-U[35]	DESCRIPTION	REFERENCE
First GP consult	414.50[36]	125-600	Dg and drug prescr.	(NGPA 2006)
GP consultation	379.50[37]	125-600	Primary care	(NGPA 2006)
Specialists consult.	416.00[38]	266-600	Secondary care	(NGPA 2006)
Citalopram 20mg	2.24[39]	1.79-2.68[40]	Daily defined dose	Footnote 15
Escitalopram 10mg	6.35[41]	5.08-7.62	Daily defined dose	Footnote 16
SNRI	9.58[42]	7.66-11.49	Daily defined dose	Footnote 15
Increased Cital dose	3.19	2.55-3.83	42,3% incr. for cital	(Lepola, Loft et al. 2003)
Increased Escit dose	8.89	7.11-10.67	40% incr. for escit	(Lepola, Loft et al. 2003)
Maintenance cit.	403.20[43]	322.6-483.8	[44]prevent new episode	Footnote 15
Maintenance escit.	1 143.00[45]	914.4-1371.6	Footnote 36	Footnote 15
Maintenance SNRI	1 724.40[46]	1379.2-2069.2	Footnote 36	Footnote 15
Mainten.increas.cit.	574.20[47]	459.36-689.04	Footnote 36	Footnote 21
Mainten.increas.esc.	1 600.20[48]	1280.1-1920.24	Footnote 36	Footnote 22
Cost day hospit.	7 000	3000-8000	LDPS/TDPS/VDPS	Footnote 23
Aver.year/ cost/pat	27 253.00[49]	22000-35000	LDPS/TDPS/VDPS	Footnote 23
Afipram for AE	4.10[50]	3.28-4.92	Treat nausea	Footnote 23
ECG (before switch)	65.00	40-125[51]	Due to cardiotoxicity	(NGPA 2006)
Production loss[52]	1 460.00	1309.35-2164.95[53]	Aver./day/salary	www.ssb.no, 2006

35 Lower and upper limit for the sensitivity analysis

36 GP's fee for prescribing drug added (takst 1h, page 16,GP fee schedule 2006/2007)

37 81.50(1/4 of capit. fee) +125(first 15 min)+108(fee next 15 min)+65.00(spec.GP fee)=379.50

38 266+150=416

39 Costs of all drugs in analysis calculated on a regular basis of sales price for three largest Norwegian pharmacy chains Vitus Apotek, Apoteke 1 and Alliance Apoteket, for one DDD (e.g. citalopram 98 tbl/20 mg= 219/98=2.24). Asked for prices 28.3.-30.3.2007

40 Lower and upper limit for the sensitivity analysis is +/-20% for the all drug prices

41 10 mg= 6.35 (622.5/98 tbl). For details, see footnote nr 39.

42 Venlafaxine (Efexor®) 75 mg DDD. NOK 938.50/98 tbl=9.58

43 DDD citalopram=2.24*180=403.20

44 6 months after symptoms reduction, maintanance to prevent new depressive episode

45 DDD escitalopram=6.35*180=1143

46 Venlafaxine DDD= 9.58*180 days= 1724.40

47 Increased citalopram dose=3.19*180=574.20

48 Increased escitalopram dose=8.89*180=1600.20

49 Per Arne Holman, Lovisenberg Diakonnale Psychiatric Hospital, Oslo, interviewed 23.3.2007

50 Afipram (metoklopramid) for nausea. NOK 68.10/50 tbl=1.362 per tbl*3 daily= NOK 4.086 per day

51 NOK 40 from www.legemiddelverket.no/upload/28350/Publisert%20rapport%20-%20mars%202007.pdf

52 Nr of days lost from work at prim. care 7 days, sec care 15 days (average 11 days). Assumption based on the study by Lepine et al 1997

53 Average monthly salary for industrial worker in Norway in 12/2006 was NOK 26187/20 days=NOK 1309.35 daily. For leaders, monthly salary was 43299/20=NOK 2164.95 daily

2.5. Sensitivity analysis

The robustness of the results was tested in the univariate sensitivity analysis on costs and probabilities and from the societal perspective. I have used two intervals. Lower and upper limits used in the sensitivity analysis are in Table 4 for probabilities, Table 5 for frequences of resources used and Table 6 for costs. Table with all parameters and lower and upper limits used in the model is in Appendix II (from Tree Age Pro). Table with results from the one-way sensitivity analysis are in the Appendix III.

3. Results

3.1. Health care payer perspective

From the health care payer perspective, the average costs per patient in the escitalopram group was NOK 5171 while in the citalopram group this costs was NOK 3911. The incremental (additional) cost per patient treated with escitalopram was NOK 1260. In the escitalopram group it was expected that drug will be effective in 84.7% of the patients, while in the citalopram group it was expected to be effective in 80.0% of the patients. Thus, expected incremental effects was 4.7%. When incremental costs are divided by incremental effects, result is expressed in term of the incremental cost-effectiveness ratio (ICER).

$$ICER = \frac{\Delta C}{\Delta E} = \frac{1259.8}{0.0466} = 27035$$

From a health care payer perspective, the cost per additional patient with reduced symptoms was NOK 27035 when citalopram was replaced by escitalopram.

Table 7 Results for the health care payer perspective

Strategy	Cost[54]	Incr Cost[55]	Eff	Incr Eff	C/E	ICER
Citalopr 20 mg	3 911		0.801		4 881	
Escitalopr 10 mg	5 171	1 259	0.848	0.047	6 098	27 035
TABLE 2 - all options refer. to a common baseline						
Citalopr 20 mg	3 911		0.801		4 881	
Escitalopr 10 mg	5 171	1 259	0.848	0.047	6 098	
TABLE 3 - ordered by increasing effectiveness						
Citalopr 20 mg	3 911		0.801		4 881	
Escitalopr 10 mg	5 171		0.848		6 098	

55 Incremental costs in NOK

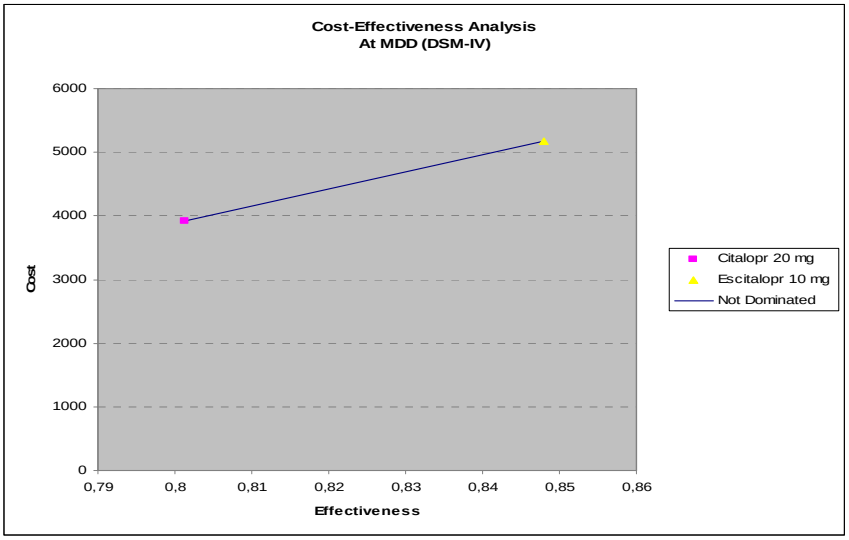

Figure 8 Cost-effectiveness of replacing citalopram by escitalopram. Health care payer perspective. No strategy is clearly dominated by other (because escitalopram is more costly and more expensive). [56]

3.2. Societal perspective

From the societal perspective, the expected average costs for one patient in the escitalopram group was NOK 20 561 while in citalopram group this costs was NOK 19 695. The incremental (additional) cost per treated patient with escitalopram was NOK 865. Expected effectiveness was the same as in the health care payer perspective, but the costs have changed; in the escitalopram group it is expected that drug will be effective in 84.7% of the patients, while in the citalopram group it was expected to be effective in 80% of the patients. As a result, incremental effects are 4.7%. When incremental costs are divided by incremental effects, the result is expressed in terms of the incremental cost-effectiveness ratio (ICER).

$$ICER = \frac{\Delta C}{\Delta E} = \frac{865.64}{0.0466} = 18575$$

From a societal perspective, the cost per additional patient with reduced symptoms was NOK 18 575 when citalopram was replaced by escitalopram.

Table 8 Results for the societal perspective

Strategy	Cost	Incr.costs (NOK)	Effect.	Incr Eff	C/E	ICER
Citalopr 20 mg	19 695		0.801		24 578	
Escitalopr 10 mg	20 561	866	0.848	0.047	24 248	18 575
TABLE 2 - all options ref. to a common baseline						
Citalopr 20 mg	19 696		0.801		24 578	
Escitalopr 10 mg	20 561	866	0.848	0.047	24 248	
TABLE 3 - ordered by increasing effectiveness						
Citalopr 20 mg	19 696		0.801		24 578	
Escitalopr 10 mg	20 561		0.848		24 248	

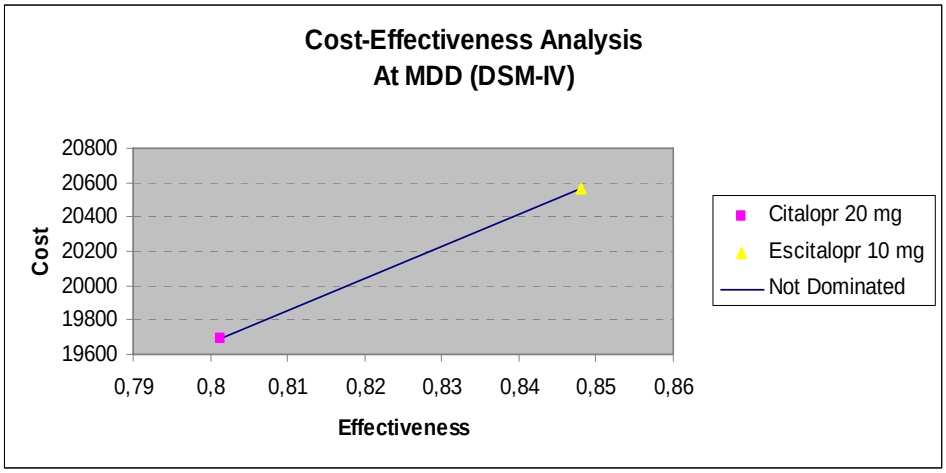

Figure 9 Cost-effectiveness of replacing citalopram by escitalopram. Societal perspective.

56 An option is dominated if it is more costly and less effective than comparator.

3.3. Cost-utility analysis

Cost-utility analysis is a useful technique because it provides a generic outcome measurement which enables comparison of the costs and health outcomes across different health care programmes. In order to express results of my analysis in terms of *cost per QALY gained*, I have used utility weights for the major depressive disorder from three different studies. (Mauskopf and Simon 2006)

Table 9 Studies with the utility weights for MDD, from the meta-analysis by Mauskopf

AUTHOR	METHOD	N	TIME	BASE U	ΔIN U *REMISSION*	Δ IN U *NO RESPONSE*
Lanert et al 2000[57]	SG	140	1 year	-	0.042	-0.012
(Sapin, Fantino et al. 2004)	EQ-5D	250	2 m.	0.3-0.35	0.5	0.28
(Pyne, Sieber et al. 2003)	QWB-SA	58	4 m.	0.41-0.425	0.201	0.021

In my model, the treatment benefit is expressed in terms of "successfully treated depression" (*symptoms reduced*) after a 6-month period. On the basis of the study by *Pyne, Sieber et al 2003*, I assume that the average difference in utility between successful and unsuccessful treatment is 0.22[58]. This means that the *QALY gain from successful treatment* is 0.22*0.5=0.11; due to half a year time perspective of my study. Consequently, cost per QALY gained for the health care payer perspective is NOK 245 000.[59] Using the same methodology and assumption, cost per QALY gained for the societal perspective is NOK 169 000.[60] If NOK 350 000 were chosen as the cost-effectiveness threshold, escitalopram is cost-effective.

57 Lanert has not reported baseline utility, therefore I have not used utility weights from his study.

58 0.5-0.28=0.22

59 ICER for health care payer perspective is NOK 27000/0.11= NOK 245 454

60 ICER for societal perspective is NOK 18600/0.11=NOK 169000

Using the value 0.18[61] for the average difference in utility between successful and unsuccessful treatment based on the study by ***Sapin et al 2004, QALY gain from successful treatment*** is 0.18*0.5=0.09; due to half a year time perspective of my study.
Thus, cost per QALY gained for the health care payer perspective is NOK 300 000.[62] For the societal perspective, cost per QALY gained is NOK 207 000. [63] Escitalopram is cost-effective.

Using utilities from the study by *Lanert et al 2000* under the assumption that the average difference in utility between successful and unsuccessful treatment is 0.054*0.5=0.027 is the *QALY gain from the successful treatment* due to 6-month time of my study, cost per QALY gained is NOK 1000 000 for the health care payer perspective.[64] Thus, for the societal perspective, under the same assumptions and using the same methodology, cost per QALY gained is NOK 690 000. Escitalopram is not cost-effective.

Table 10 Results of the cost-utility analysis

REFERENCE	INSTRUMENT [65]	QALYS GAIN[66]	COST PER QALY, SOCIETAL PERSPECTIVE	COST PER QALY, HEALTH CARE PAYER PERSPECTIVE	COST-EFF. OF ESCIT IF TRESHOLD IS NOK 350000[67]
Pyne et al 2003	**QWB-SA**	**0.11**	**169 000**	**245 000**	**Yes**
Sapin et al 2004	EQ-5D	0.09	207 000	300 000	Yes
Lanert	SG	0.027	690 000	1 000 000	No
Difference[68]	-	*0.083*	*521 000*	*755 000*	-

The results in terms of *costs per QALY gained* depend on utility gain from the successful treatment. Hence these utilities depend on the instrument used. The study by Pyne assessed utility weights at four months by the *quality of well-being scale (QWB-SA).*

61 0.201-0.021=0.18

62 27000/0.09=300 000

63 18600/0.09=206 666

64 ICER 27000/0.027=1000 000

65 Instrument used to assess utility weights for depression

66 QALYs gain from succesful treatment, as difference from the change in utility when remission- change in utility when no response

67 Kristiansen, I. S., D. Gyrd-Hansen, et al. (2007). "[Prioritization and health--should maximum-price life years be introduced?]." Tidsskrift for Den Norske Laegeforening **127**(1): 54-7.

68 Difference between the lowest to the highest utility value

When these utility weights were used in my analysis, cost per QALY gained was NOK 169 000 for the societal perspective and NOK 245 000 for the health care payer perspective. Escitalopram is a cost-effective option.

Study by Sapin used EQ-5D *(quality of life five-dimension instrument)* which tend to overestimate utilities. Cost per QALY gained using Sapin's utility weights was NOK 207 000 for the societal and NOK 300 000 for the health care payer perspective. Escitalopram is a cost-effective option.

Lanert have used the *standard gamble method,* which has resulted in the lowest utility values after one year when compare to other two studies by Pyne and Sapin. Consequenlty, the lowest change in the utility weights led to the highest cost per QALY gained of NOK 690 000 for the societal and NOK 1 000 000 for the health care payer perspective. Considering the treshold for *cost per QALY gained* which is NOK 350 000 in Norway, escitalopram is not a cost-effective option over citalopram.

I have decided to use results based on the utility change by from the study Pyne, because of advantages of that study compared to Sapin and Lanert: choice of the instrument was Self-Administered Quality of Well-being Scale (QWB-SA) which does not overestimate utility weights as EQ-5D does and study duration was four months, which is reasonable since my model has a time of six months. It is remarkable that cost per QALY gained among the three scenarios differ for about NOK 500 000 in the societal perspective and even NOK 755 000 in the health care payer perspective.[69] This emphasizes the importance of the instrument choice in collecting utility weights.

69 Difference between the lowest to the highest utility value

3.3. Sensitivity analysis results

In one-way sensitivity analyses on all parameters (costs and probabilities), the results were, in the societal perspective, robust for all the parameters except for the *probability of a good response in the escitalopram group*. This parameter had value of 0.44 with lower bound of 0.39 and upper limit of 0.49. When lower bound (0.39) was used for good response rate in escitalopram group, this affected results so that escitalopram was not cost-effective any longer but it was dominated by citalopram. (Appendix III)

The results were not sensitive to changes in the unit costs. Largest variation in ICER appeared at probability of no response to citalopram at week 8. Here the difference between lower and upper ICER was NOK 230 000.

Changes in assumptions about productivity costs (where the assumptions for lower and upper limit were based on the average number of working days lost due to depression in six-month period) resulted in variation in ICER of NOK 8 400 for the primary care patients and NOK 19 000 for the secondary care patients.

4. Discussion

The results of the cost-utility analysis suggest that escitalopram is cost-effective in treating major depressive disorder in Norway. CUA resulted in the cost per QALY gained of NOK 169 000 for the societal and NOK 245 000 for the health care payer perspective. For both perspectives cost per QALY gained was under the threshold of NOK 350 000.

The utility gain from depression treatment of 0.11 that I used in this study might not be the best estimate of utility gain for depressed patients treated with citalopram and escitalopram. The study by Pyne assessed utility weights from relativelly small number of patients (n=58). Therefore my conclusions which are based on these utilities should be taken with caution.

Study limitations

Limitations in the studies occurs due to complexity of the pharmacoeconomics and a lack of a generally accepted methodology. (Pirraglia, B. et al. 2004) There has been lack of guideliness for economic evaluation in Norway and there is no consensus among analysts as to what should be included in the analysis. In addition, there is no standardized cost database for Norway.

Another limitation comes from the use of the RCTs as the source of the effectiveness data. When pharmaceutical companies fund RCT they avoid to enroll patients with severe depression because to have mildly/moderately depressed patients in trial might result in better effectiveness of the new drug. Around one third of patients in the trials fail to complete the trial so it seems that only patients to whom the drug *works* remain in the trial and the number of serious adverse events might be underestimated. Besides the short duration of clinical trials on citalopram and escitalopram, RCTs did not measured utilities so I had to tranfer utility weights into QALYs.

The main limitation of my model is a six-month time perspective. Cost-effectiveness of the treatment of MDD depends on the success of the treatment in the long run while RCT on citalopram and escitalopram show efficacy in the short period (mostly for only eight and 14 weeks, only one trial lasted for 24-weeks). The 24-week head-to-head clinical trial of citalopram and escitalopram used in my model included 357 adults that were under age of 65.

(Colonna, Andersen et al. 2005) This is also limitation since an aging population in Norway represents a large group of patients that use citalopram and escitalopram.

In the societal perspective I have used productivity costs based on average days that employed persons loses from work due to depression. In order to capture broader societal costs, analysis can use e.g. travel costs and costs of time lost by the depressed person's family members. These costs are not included in my analysis.

Reviews of the literature that I have used to assess effectiveness data did not validate the quality of each of the reviewed studies. One-way sensitivity analyses is performed; changing one variable at a time is not realistic but it gives us an idea of which of the model parameters might have the strongest influence on results.

Strengths of the study

This study was not funded by anyone and the author did not have any interest in presenting any of drugs as cost-effective. I have used cost data for 2006-2007 and empirical data for average yearly costs per patient at the psychiatric hospital in Oslo.

The model has some improvements when compared to some previous ones, and some limitations as well. Other models were separated primary and secondary care. Because the patient begins in the primary care and goes to secondary, in many cases he will go back and forth as depression changes. Therefore I see a strict distinction between primary and secondary care as unnecessary. Further, published CEA on citalopram vs. escitalopram lack the comparative clinical data between two drugs. (e.g. Francois et al 2003)

In calculating productivity loss, other studies have used assumptions that all patients work. Productivity costs in my study were based on the average loss of working days during six months for depressed person. Using utility weights and expressing results in *cost per QALY* it is possible to compare results to other analyses.

Comparison with other cost-effectiveness studies

Comparing my results with the other CEA that analysed cost-effectiveness of citalopram and escitalopram, the conclusion that escitalopram is cost-effective does not differ. All studies (Table 11) were funded by Lundbeck. In the study by Kulp from 2005 it is not clear whether study is funded and by whom. Kulp has used a Markov model while other studies used a two-path decision tree.

Table 11 Other cost-effectiveness studies results

REFERENCE	COUNTRY	COMPARATORS	ANALYSIS/MODEL/ PERSPECTIVE	CONCLUSION
(Demyttenaere, Hemels et al. 2005)	Belgium	escitalopram,citalopram, venlafaxine	CEA/decision tree	Escitalopram is cost-effective
(Francois, Toumi et al. 2003)	Norway	escitalopram,citalopram, fluoxetine,venlafaxine	CEA/decision tree	Escitalopram is cost-effective.
(Kulp, von der Schulenburg et al. 2005)	Germany	escitalopram, venlafaxine	CEA/markov model (70 days)	Escitalopram is "preferable" to venlafaxine
(Hemels, Kasper et al. 2004)	Austria	escitalopram, vs. citalopram	CEA/decision tree	Escitalopram is cost-effective from the societal perspective
(Wade, Toumi et al. 2005)	UK	escitalopram,venlafaxine, citalopram	CEA/decision tree	Escitalopram is cost-effective compared to citalopram but not compared to venlafaxine

Policy implications

Based on this analysis society should fund escitalopram for treatment of depression in Norwegian adults as it appeared cost-effective from societal and health care payer perspective. Although the price of escitalopram is relatively high, cost savings compensate for the drug price, especially in societal perspective.

Escitalopram should not be seen as expensive for society because it might improve patients' quality of life, increase their social functioning and ability to work. Analysis results indicate the need for increasing the daily defined dose of citalopram 20 mg and escitalopram 10 mg. Sufficient dose at the beginning of the treatment might save costs later. It might be useful to re-evaluate daily defined doses for citalopram and escitalopram. Costs of an increased dose of

the drug might be lower than costs of increased resource use caused by an insufficient minimal daily dose.

The results of this decision analysis indicate that three types of data are needed to reduce the uncertainty about the cost-effectiveness of escitalopram. First we need trials of 1-5 years of follow-up because depression is a chronic disease. Such trials would provide more accurate data on the probabilities of the model. Second, we need data on quality of life captured in a long-term trial, preferably with the TTO or a similar method. This would provide better data on utilities for different depression health states. Third, we need more data on how patients in practice are treated for major depression in Norway.

The results demonstrate that escitalopram is likely to be a cost-effective option in the short-run. Based on my analysis I do not have evidence to draw conclusions about the long-run cost-effectiveness of escitalopram (1-5 years).

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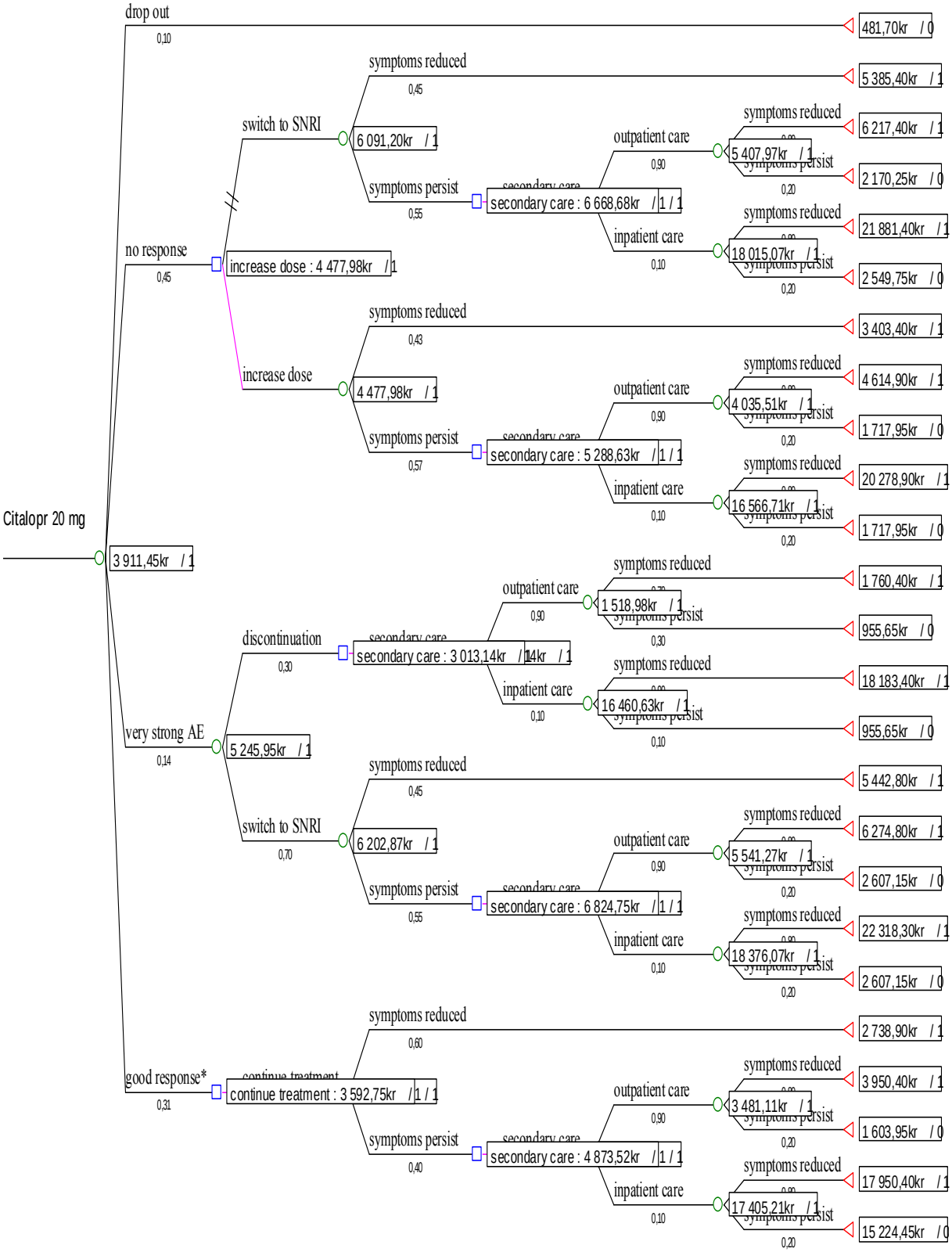
Stockholm, The Swedish Council on Technology Assessment in Health Care

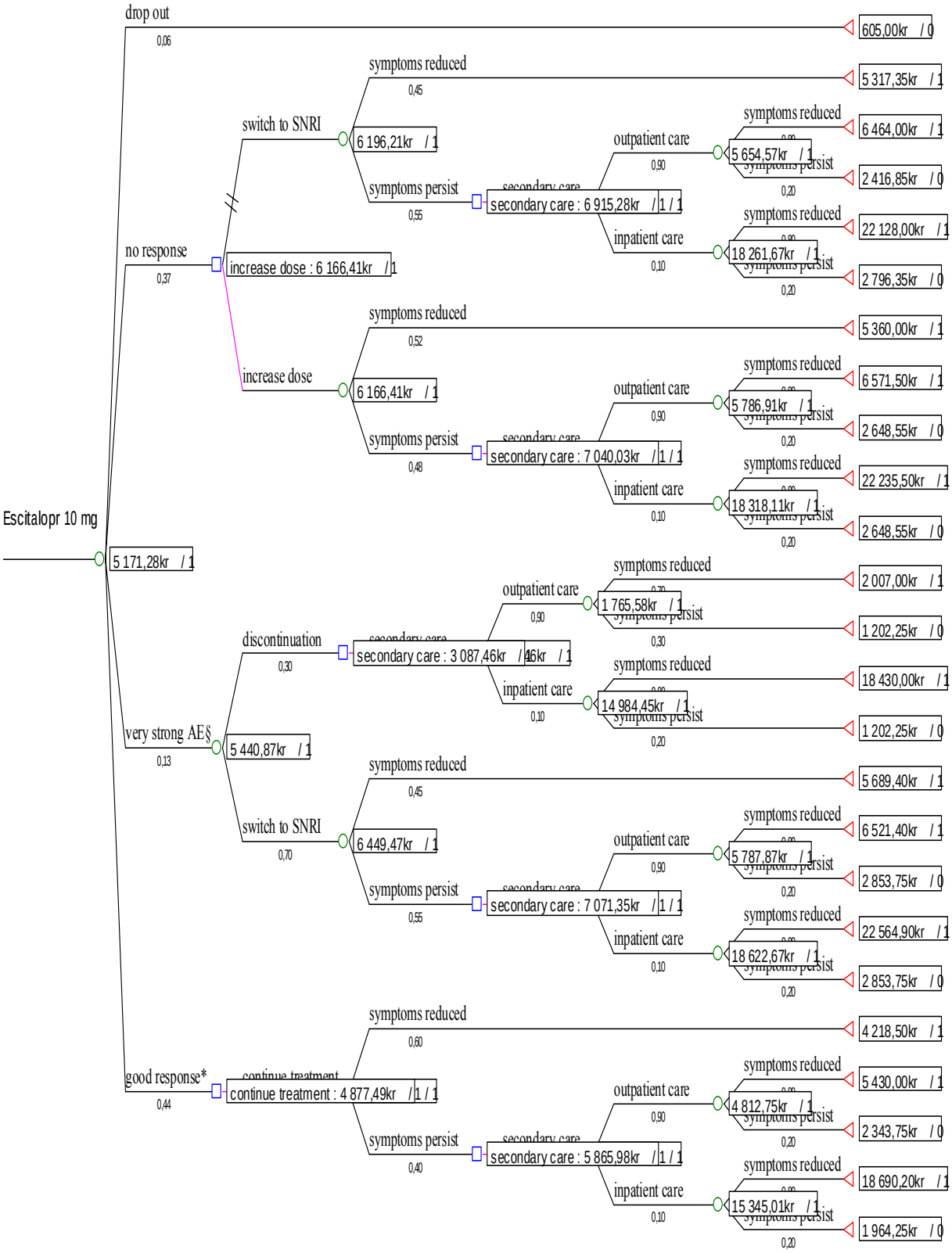
6. List of figures and tables

Appendix I Rolled-back tree

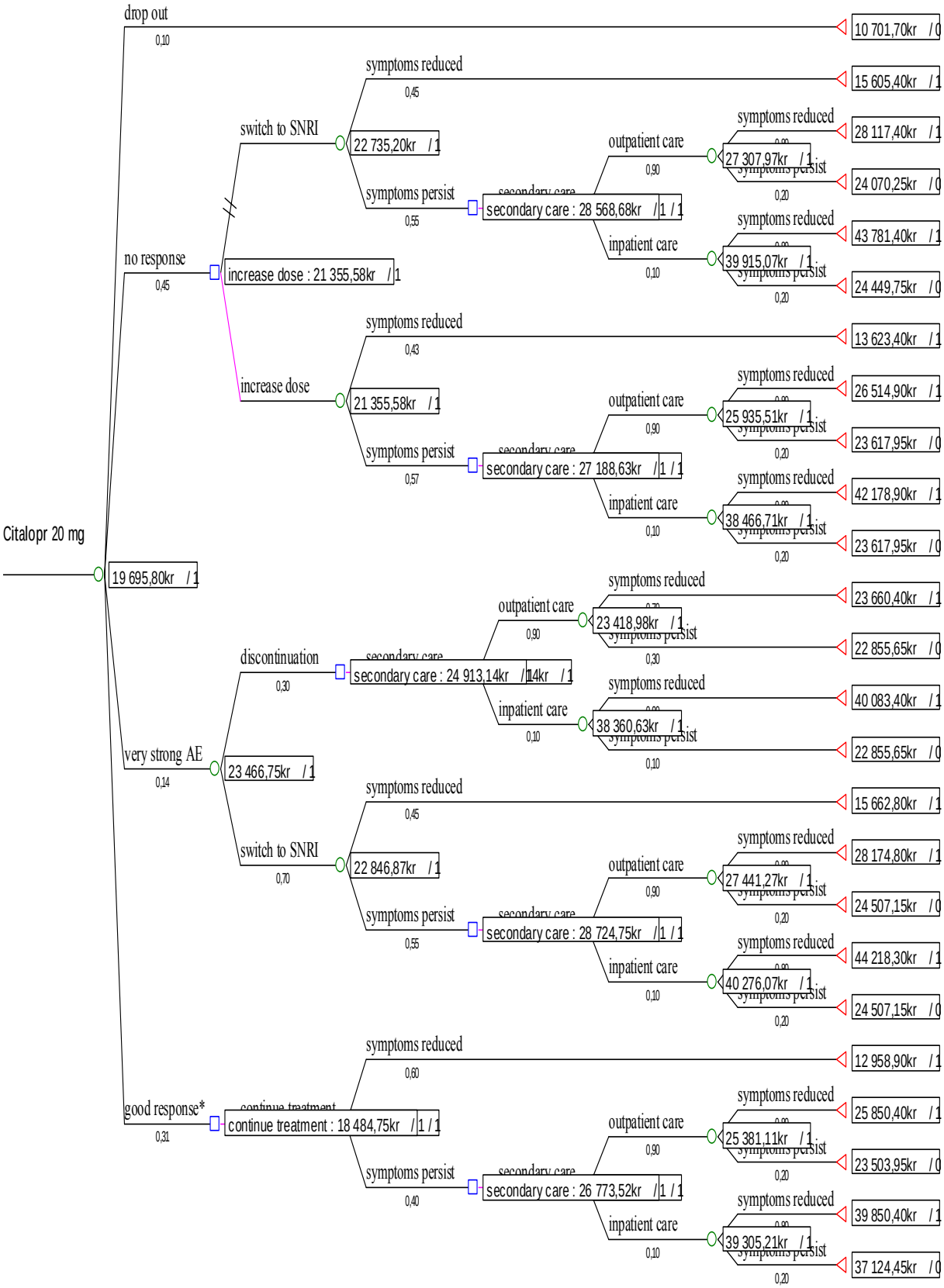
Expected values, citalopram node, health care payer perspective



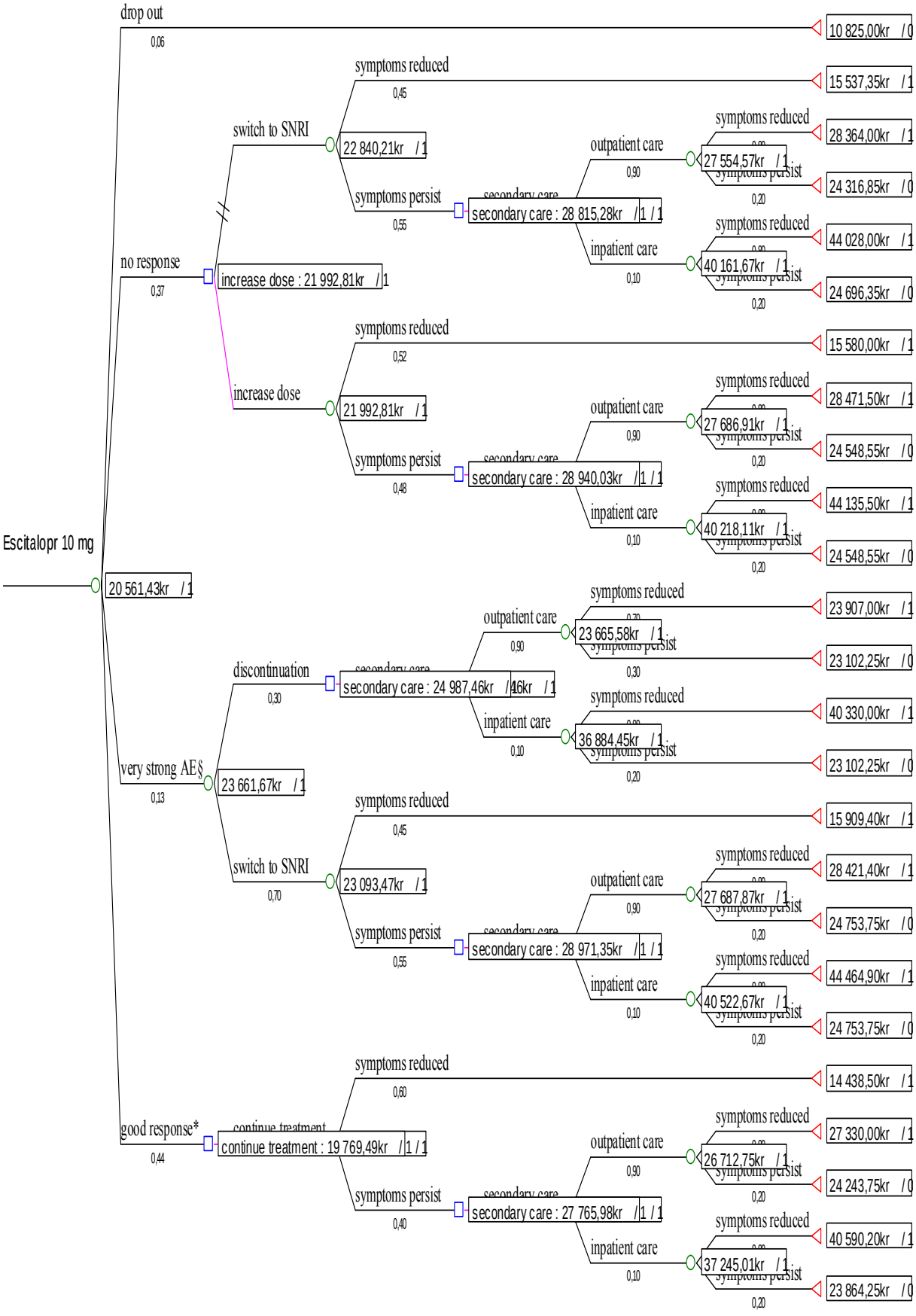
Expected values, escitalopram node, health care payer perspective



Expected values, citalopram node, societal perspective



Expected values, escitalopram node, societal perspective



Appendix II Parameters used in the model

Health care payer perspective

Parameters, values and lower and upper range			
Name	Value	Low	High
cAver_yr_patient_psychiatry	27,253	22000	35000
cDaily_afipram_for_side_eff	4,1	3,28	4,92
cDDD_cital_20mg	2,24	1,79	2,68
cDDD_escital_10mg	6,35	5,08	7,62
cDDD_SNRI	9,58	7,66	11,49
cECG_before_venlafaxine	65	40	125
cFirstGP_visit_diagnostics	414,5	125	600
cGP_visit	379,5	125	600
cInceras_escital14mg	8,89	7,11	10,67
cIncreas_cital_28mg	3,19	2,55	3,83
cSpecialist_consult	416	266	600
c_day_hospital	7000	3000	8000
c_Increas_SNRI_100mg	0		
c_maintenanceSNRI	1724,4	1379,2	2069,2
c_maintenance_cital	403,2	322,6	483,8
c_maintenance_escit	1143	914,4	1371,6
c_maintenance_increased_escit	1600,2	1280,1	1920,24
c_maintenance_increas_cital	574,2	459,36	689,04
fSpec_consul_when_hospitalization	6	3	9
f_GPvisits_during_maintenance	4	1	6
f_GPvisit_if_sympt_reduced	2	1	4
f_spec_consult_if_sympt_persist	4	2	8
f_spec_consult_if_sympt_reduced	2	1	3
nr_of_days_on_afipram	14	7	30
pdrop_out_cital	0,1	0,06888	0,13112
pdrop_out_escit	0,06	0,035364	0,084636
pgoodresponse_cital	0,31	0,262024	0,357976
pgoodresponse_escit	0,44	0,388508	0,491492
p_AEstrong_cital	0,14	0,104006	0,175994
p_AEstrong_escit	0,13	0,095114	0,164886
p_discontin_cit	0,3	0,252463	0,347537
p_discontin_escit	0,3	0,252463	0,347537
p_inpatient_cital	0,1	0,06888	0,13112
p_inpatient_escital	0,1	0,06888	0,13112
p_noresponse_cit	0,45	0,398393	0,501607
p_noresponse_escit	0,37	0,319917	0,420083
p_outpatient_second_care_cit	0,9	0,86888	0,93112
p_outpatient_second_care_escit	0,9	0,86888	0,93112
p_switch_after_strong_AE_cit	0,7	0,652463	0,747537
p_switch_after_strong_AE_escit	0,7	0,652463	0,747537
p_sympt_pers_after_discont_cit	0,3	0,252463	0,347537
p_sympt_pers_after_discont_escit	0,3	0,252463	0,347537
p_sympt_pers_after_goodresp_cit	0,4	0,349181	0,450819
p_sympt_pers_after_goodresp_escit	0,4	0,349181	0,450819
p_sympt_pers_after_increase_cit	0,57	0,518644	0,621356

p_sympt_pers_after_increase_escit	0,48	0,428174	0,531826
p_sympt_pers_after_outpat_cit	0,2	0,158506	0,241494
p_sympt_pers_after_outpat_escit	0,2	0,158506	0,241494
p_sympt_pers_after_switch_cit	0,55	0,498393	0,601607
p_sympt_pers_after_switch_escit	0,55	0,498393	0,601607
p_sympt_red_after_discont_cit	0,7	0,652463	0,747537
p_sympt_red_after_discont_escit	0,7	0,652463	0,747537
p_sympt_red_after_goodresp_cit	0,6	0,549181	0,650819
p_sympt_red_after_goodresp_escit	0,6	0,549181	0,650819
p_sympt_red_after_increase_cit	0,43	0,378644	0,481356
p_sympt_red_after_increase_escit	0,52	0,468174	0,571826
p_sympt_red_after_inpat_cit	0,8	0,758506	0,841494
p_sympt_red_after_inpat_escit	0,8	0,758506	0,841494
p_sympt_red_after_outpat_cit	0,8	0,758506	0,841494
p_sympt_red_after_outpat_escit	0,8	0,758506	0,841494
p_sympt_red_after_switch_cit	0,45	0,398393	0,501607
p_sympt_red_after_switch_escit	0,45	0,398393	0,501607
qdays_cital_before_discontinuat	60	30	90
qdays_escit_before_discontinuat	60	30	90
qdays_on_cital_before_dropout	30	7	60
qdays_on_escit_before_dropout	30	7	60
q_days_good_resp_cital	180	60	360
q_days_good_resp_escit	180	60	360
q_days_on_cital_before_increase	60	30	90
q_days_on_escit_before_increase	60	30	90
q_days_on_switched_SNRI	120	60	160
q_of_days_in_hospital	2	1	7
q_of_days_on_cital_before_switch	60	30	80
q_of_days_on_escit_before_switch	60	30	80
q_of_days_on_increased_cital	120	40	180
q_of_days_on_increased_escit	120	40	180

Societal perspective

q_workdays_lost_primarycare	7	2	10
q_workdays_lost_secondarycare	15	5	21
cProductDayFromWork	1460	1309,35	2164,95

Appendix III One-way sensitivity analysis results

Name	Description	Lower	Upper
cAver_yr_patient_psychiatry	average cost per pat yearly,3 psych hospit Oslo	15283	13343
cDaily_afipram_for_side_eff	daily cost of afipram	18566	18562
cDDD_cital_20mg	cost of 20 mg citalopram DDD	19465	17682
cDDD_escital_10mg	cost of DDD escitalopram,10 mg	15566	21562
cDDD_SNRI	DDD 75 mg venlafaxine (Efexor in Norway)	18598	18530
cECG_before_venlafaxine	due to cardiotoxicity of the drug	18568	18555
cGP_visit	cost for one GP visit in Norway	18090	18974
cInceras_escital14mg	dose can be increased to 20 mg daily	16883	20245
cIncreas_cital_28mg	28 mg of citalopram cost	19300	17829
cProductDayFromWork	day that patient is out of job due to depression	19429	14516
cSpecialist_consult	consultation with specialist in psychiatry	18823	18247
c_day_hospital	inpatient care psychiatric clinic	19445	18345
c_maintenanceSNRI	if reduced sympt,continue therapy for 6 months	18610	18518
c_maintenance_cital	6 months after symptom red,to prevent relapse	19029	18100
c_maintenance_escit	6 months after symp red,to prevent relapse	16664	20463
c_maintenance_increased_escit	6 months after sympt red, to prevent relapse	16287	20840
c_maintenance_increas_cital	6 months maint on incr dose of citalopram	19299	17829
fSpec_consul_when_hospitalization	Frequency of special consult if inpatient care	18746	18382
f_GPvisits_during_maintenance	during 6 months of maint. pat will visit the GP	17374	19357
f_GPvisit_if_sympt_reduced	Freq of GP visits when sympt are reduced	18740	18388
f_spec_consult_if_sympt_reduced	Freq of specialist consult when sympt reduced	18740	18388
nr_of_days_on_afipram	drug used by patients who have AE (nausea)	18568	18554
pgoodresponse_cital	probability of good response for citalopram	13672	173302
pgoodresponse_escit	prob of the good response for escitalopram	**DOMINATED**	14127
p_AEstrong_cital	very strong adverse effects, poor tolerability	17254	24530
p_AEstrong_escit	prob that escit will have very strong adv. effects	23805	17335
p_noresponse_cit	at week 8 no response to drug	15340	249234
p_noresponse_escit	at week 8 no response to drug	179690	15517
p_outpatient_second_care_cit	Pat will be treated as outpat in citalopram group	14509	22596
p_outpatient_second_care_escit	patient will be tr. as outpatient in escit group	21973	15137
p_switch_after_strong_AE_cit	prob of switching due to adverse events on cit	17841	19324
p_switch_after_strong_AE_escit	prob of switch due to adverse events on escit	19268	17892
p_sympt_pers_after_goodresp_cit	symp are still persist after pat resp well on cit	24859	13060
p_sympt_pers_after_goodresp_escit	symp persist after pat resp well on escit	11164	27519
p_sympt_pers_after_increase_cit	symp will still pers after cital dose is increased	27982	10832
p_sympt_pers_after_increase_escit	symp will still pers after escit dose is increased	27982	10832
p_sympt_pers_after_switch_cit	symp will persist after cit will be switched	20408	16798
p_sympt_pers_after_switch_escit	sympt will persist after escit will be switched	16921	20273
p_sympt_red_after_discont_cit	sympt will be red after pat has discont cit	17910	19270
p_sympt_red_after_discont_escit	sympt will be red after pat disc treat with escit	19217	17955
p_sympt_red_after_inpat_cit	sympt will be red after pat in cital to sec care	5952	18744
p_sympt_red_after_inpat_escit	symp will be red after pat escit go to sec care	5037	6069
p_sympt_red_after_outpat_cit	after outp care,prob that pat will have sympt red	5035	26849
p_sympt_red_after_outpat_escit	after outpat care pat will have symptom red	6597	5062
qdays_cital_before_discontinuat	Nr of days on citalo before discontinuation	18624	18504
qdays_escit_before_discontinuat	Nr of days on escit before discontinuation	18405	18721
qdays_on_cital_before_dropout	drop out, measured at week 4	18674	18420
qdays_on_escit_before_dropout	Number of days on escit before drop out	18377	18807
q_days_good_resp_cital	nr days when good response to citalopram	20336	15906

q_days_good_resp_escit	nr of days when resp good to escitalopram	11433	29260
q_days_on_cital_before_increase	Nr of days on citalopr before increased dose	19207	17921
q_days_on_escit_before_increase	Nr of days on escitalopr before increased dose	17065	20063
q_days_on_switched_SNRI	nr of days on venlafaxine	18650	18507
q_of_days_in_hospital	average nr of days spent inpatient	19335	14708
q_of_days_on_cital_before_switch	Nr of days on citalopram before switch	18704	18470
q_of_days_on_escit_before_switch	Nr of days on escitalopram before switch	18195	18810
q_of_days_on_increased_cital	Nr of days on increased citalopram	21006	16732
q_of_days_on_increased_escit	Nr of days on increased escitalopram	12968	22761
q_workdays_lost_primarycare	nr of days pat have lost from work primary c.	13324	21708
q_workdays_lost_secondarycare	nr of days patient has lost, by using sec. Care	31096	12276

Appendix IV MADRS questionnaire

MADRS

(MONTGOMERY AND ASBERG DEPRESSION RATING SCALE)

Br. J. Psychiat. (1979), 134, 382-389

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. The items should be rated with regards to how the patient has done over the past week.

1 - APPARENT SADNESS - *Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.*

0 No sadness

1

2 Looks dispirited but does brighten up without difficulty

3 ☐

4 Appears sad and unhappy most of the time

5

6 Looks miserable all the time. Extremely despondent.

2 - REPORTED SADNESS - *Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.*

0 Occasional sadness in keeping with the circumstances.

1

2 Sad or low but brightens up without difficulty.

3 ☐

4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.

5

6 Continuous or unvarying sadness, misery or despondency.

3 - INNER TENSION - *Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.*

0 Placid. Only fleeting inner tension.

1

2 Occasional feelings of edginess and ill-defined discomfort

3 ☐

4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.

5

6 Unrelenting dread or anguish. Overwhelming panic.

4 - REDUCED SLEEP - *Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.*

0 Sleeps as usual.

1

2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep

3 ☐

4 Sleep reduced or broken by at least two hours.

5

6 Less than two or three hours sleep.

5 - REDUCED APPETITE - *Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.*

0 Normal or increased appetite.

1

2 Slightly reduced appetite

3

4 No appetite. Food is tasteless.

5

6 Needs persuasion to eat at all.

6 - CONCENTRATION DIFFICULTIES - *Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.*

0 No difficulties in concentrating.

1

2 Occasional difficulties in collecting one's thoughts.

3

4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.

5

6 Unable to read or converse without great difficulty.

7 - LASSITUDE - *Representing a difficulty getting started or slowness initiating and performing everyday activities.*

0 Hardly any difficulties in getting started. No sluggishness.

1

2 Difficulties in starting activities.

3

4 Difficulties in starting simple routine activities, which are carried out with effort.

5

6 Complete lassitude. Unable to do anything without help.

8 - INABILITY TO FEEL - *Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure.The ability to react with adequate emotion to circumstances or people is reduced.*

0 Normal interest in the surroundings and in other people.

1

2 Reduced ability to enjoy usual interests.

3

4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.

5

6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9 - PESSIMISTIC THOUGHTS - *Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.*

0 No pessimistic thoughts.

1

2 Fluctuating ideas of failure, self-reproach or self-depreciation.

3

4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.

5

6 Delusions of ruin, remorse and unredeemable sin. Self-accusations which are absurd and unshakable.

10 - SUICIDAL THOUGHTS - *Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.*

0 Enjoys life or takes it as it comes.

1

2 Weary of life. Only fleeting suicidal thoughts.

4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.

6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.